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Report of the 2008 Education Committee panel on "Teaching Safety in the OR"

Daniel B. Jones

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Abstract
Introduction At the 2008 Digestive Diseases Week, the Education Committee of the Society for Surgery of the Alimentary Tract sponsored a symposium entitled "Teaching Safety in the OR."
Discussion Four panelists presented perspectives on learning from adverse events and near misses, lessons learned from aviation, who should and should not be in the operating theatre, and building better teams.
Conclusion A common theme is that we can always do better when is comes to promoting patient safety.

Keywords Patient safety · Simulation · Operating room · Surgery

Introduction

The Institute of Medicine published in 1999, "To Err is Human: Building a Safer Health Care System" and brought to the forefront concerns about patient safety in America's hospitals.[1] The authors identified nearly one-hundred thousand preventable errors. Surgeons were challenged to rethink business as usual and develop new approaches to improve safety in the operating room.

In this symposium, organized by the Education Committee of the SSAT, four panelists discussed improving safety in the OR. As surgeons, how can we best learn from errors and near misses, how does the aviation industry use simulation to improve safety, what is the role of third parties in the operating room, and how might teamwork ultimately prevent adverse outcomes? These perspectives are published in the following four articles included in this issue of the Journal of Gastrointestinal Surgery.

Perspectives

Adverse outcomes in the operating room get most of the attention, but almost as important are relatively minor errors that may happen more often and can escalate into major problems if they go unchecked. Caprice Christian Greenberg, MD, MPH discusses how the Brigham and Women's Hospital in Boston has studied "near misses" to examine how to change its systems to prevent future problems.[2] She notes that most adverse events are surgical in nature, usually occur while the patient is still in the operating room, and she therefore targets the operating room for safety research and intervention.

Richard C. Karl, MD implores surgeons to adopt a "culture" of safety from the aviation industry. As a pilot himself, Dr. Karl explains the importance of work hour restrictions, crew resource management and simulation

This introduction was originally presented as part of the SSAT Education Committee Panel on Teaching Safety in the OR at the SSAT 49th Annual Meeting, May 2008, in San Diego, California. The other articles presented in the panel were Greenberg CC, Learning from Adverse Events and Near Misses; Karl RC, Aviation; Sudan DL, Safety in the OR: Who's In and Who's Out?; and Moorman DW, Building Better Teams in Surgery.

D. B. Jones
Department of Surgery, Beth Israel Deaconess Medical Center,
Harvard Medical School,
Boston, MA, USA

D. B. Jones (✉)
Section for Minimally Invasive Surgery,
Beth Israel Deaconess Medical Center, Harvard Medical School,
Boston, MA 02215, USA
e-mail: Djones1@BIDMC.Harvard.edu

training for maintenance of skills.[3] He applauds the use of simulation for training, and he notes that the aviation industry has used flight simulators for decades without scientific proof of its effectiveness. Just as pilots go into a flight simulator and practice how to get out of difficult situations by working together, simulation can take a team of surgeons, nurses and scrub techs into a mock operating room to deal with crises.

Debra L. Sudan, MD addresses the sticky wicket of who should or should not be in the operating room. A common complaint of patients and the media is that the operating room often has people who are not members of the medical team. As professionals, we need to work to understand products before they come into the operating room. Yet, there may be good reasons for an industry representative to bring in their product the first time it is used by the surgeon. Clearly, professionals should not rely on non-professionals for our education, but sometimes, a product representative may be better able to troubleshoot their technology, as I have found all too often with our MIS teleconferencing system and laparoscopic monitors. Dr. Sudan highlights the value of using checklists and usefulness of redundancy in critical processes. She further comments on the adverse impact of the disruptive physician.

Donald W. Moorman, MD notes that while the surgeon is viewed as the head of the surgical team, other team members play key roles and must have voices in the process. Dr. Moorman emphasizes the importance of a culture shift whereby any member of the operating room team can stop the line until the team has addressed the concern in a very formal way. Dr. Moorman shares how principles have been taught with workshops at Beth Israel Deaconess Medical Center in Boston and how safe practices are reinforced using simulation training.[4] Objective metrics track success.

Summary

The presentations of the 2008 SSAT Education Committee Program espouse a culture of safety that serves as a guiding principle. Members of the team are empowered to question any issue that could conceivably adversely affect the patient. Teams must work together to communicate and problem solve. In this new culture, the surgical adage is "Patient Safety First".

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Learning from Adverse Events and Near Misses

Caprice C. Greenberg

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Keywords Adverse events · Near misses · Patient safety · Operating room · Malpractice claims

Introduction

Patient safety has received increasing attention since the Institute of Medicine (IOM) published *To Err is Human* suggesting that 3–4% of hospitalized patients will experience an adverse event. In looking closer at the etiology of these events, it is obvious that, as surgeons, we can play a major role in improving patient safety. Over half of all medical adverse events are surgical in nature and 75% of these occur in the operating room (OR). It therefore seems that the greatest improvements in patient safety will be achieved by targeting the OR for safety research and intervention.

The predominance of operative adverse events is not surprising. Not only is the OR the site of the most invasive type of medical care, it is also one of the most complex work environments in which people perform. Yet, despite a large body of literature addressing safety and coordination in other complex work environments, limited research on the OR exists.

Limitations of the Term "Error"

The IOM defines "*error*" as the failure of a planned action to be completed as intended (error of execution) or the use of the wrong plan to achieve an aim (error of planning). This IOM definition fails to describe the full range of adverse medical events because it implies that an error is a discrete action committed by a single agent and all clinicians know this is an oversimplification in most cases.

To illustrate this, we need to turn to literature from industrial safety research. James Reason describes two types of error; active and latent. *Active errors* produce an immediate, measurable change in a given patient's status. For this reason, they are easily recognized and studied. By comparison, *latent errors* are features of the patient care environment, decisions, or plans that do not produce an immediate change in patient status but set up the conditions for such events to occur. We need to focus our attention on latent errors if we want to improve patient safety. The problem is our natural tendency to associate the term "error" with "active error." This only serves to perpetuate a culture of blame and implies a discrete, identifiable fault that discourages a deeper understanding of the hidden faults and system features that contribute.

This paper was originally presented as part of the SSAT Education Committee Panel on Teaching Safety in the OR at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA, USA. The other articles presented in the panel were Jones DB, "Teaching Safety in the OR"; Karl RC, "Aviation"; Sudan DL, "Safety in the OR: Who's In and Who's Out?"; and Moorman DW, "Building Better Teams in Surgery."

C. C. Greenberg
Center for Surgery and Public Health,
Brigham and Women's Hospital,
Boston, MA, USA

C. C. Greenberg
Center for Outcomes and Policy Research,
Dana-Farber Cancer Institute,
Boston, MA, USA

C. C. Greenberg (✉)
Division of Breast Surgical Oncology,
Brigham and Women's Hospital,
75 Francis Street,
Boston, MA 02115, USA
e-mail: ccgreenberg@partners.org

A Framework for Studying Safety in the OR

In order to truly understand how adverse events occur, we need to think of the OR as a *system*, or a complex assembly of people, information, resources, and equipment working toward a common goal: the safe, effective performance of an operation. System *vulnerability* reflects exposure to events and factors that can make the system less safe or more prone to adverse events. System vulnerability increases and safety decreases as events and factors cause a deviation from the expected safe course of care. If this deviation is allowed to progress, a threshold will be crossed where patient harm occurs (an *adverse event*). If compensation occurs, the system can return to the expected course of care during the operation, either before or after patient harm (*adverse event* or *near miss*). Once compensation occurs, these events are difficult to detect and study. Because surgical providers are accustomed to compensating in a high-risk system, unsafe practices are often not recognized if the outcome is good. Yet, it is the process of care and the environment in which care is delivered that most accurately reflect the overall safety of a system (regardless of outcome) and need to be studied in order to better understand and prevent adverse events.

Methods to Identify and Study Adverse Events and Near Misses

Malpractice Claims

The landmark studies describing adverse events and near misses utilized data from closed malpractice claims. The Harvard Medical Practice Study and study of Adverse Events in Colorado and Utah provided much of the data in the IOM reports on quality and safety. While these original malpractice claims analyses were able to describe where things went wrong, they did not shed much light on how. The Medical Insurer's Malpractice Error Prevention Study (MIMEPS) was a large analysis of claims data from the Harvard School of Public Health.[1] MIMEPS confirmed that 75% of events occur in the OR but, perhaps more importantly, began to identify some of the factors that increased system vulnerability and contributed to adverse events. The two most common were technical competence and communication breakdown.

Self-reporting

Another approach to identifying adverse events and near misses relies on self-reporting. Most institutions have an online reporting system and there are several commercially available. The difficulty with these systems is that they rely on the frontline provider to recognize that safety was compromised, remember what occurred once the operation is completed, and be willing and motivated to report the event. Because of this, self-reports tend to identify serious events with bad outcomes, but as we know there is much to be learned from cases that are recovered.

One self-reporting system that has been quite successful is the Pennsylvania Patient Safety Reporting System (PA-PSRS), a statewide database maintained by the Pennsylvania Patient Safety Authority, an independent agency created by the state to reduce harm from medical errors. Reporting is mandatory and anonymous and contains no identifying information. All information is confidential, nondiscoverable, and not admissible as evidence. These features of the PA-PSRS mirror successful reporting systems in other high-risk work domains. The PA-PSRS collects over 200,000 reports per year, 97% of which are "near-miss" events.

Another approach to increasing the value of frontline providers is to proactively collect data at the time of the operation rather than passively relying on self-reporting. Using this approach, Wong and colleagues report a mean of 3.5 events that compromised patient safety per case in cardiac surgery and 90% of these were recovered making them difficult to identify.[2] Oken and colleagues compared the sensitivity for this type of proactive open-ended questioning to online self-reporting.[3] Safety-compromising events were identified in 30% of cases with prospective questioning, compared to 1.9% with self-reporting.

Prospective Field Observations

Direct observation at the point of care has the greatest potential to identify events where safety is threatened. Additionally, these studies allow for an in-depth analysis of the system factors that contribute to these events and those that help providers compensate when things start to go wrong. This type of field work is well accepted in other high-risk work environments and is beginning to be adapted to the OR. Data can be collected either by trained observers in the field or by automated data collection. The majority of this work has focused on cardiac surgery and pediatric cardiac surgery in particular. This is likely due to the inherent complexity and risk of these procedures. However, prospective field studies have also investigated safety in intensive care units, orthopedics, and general surgery. Most of this work builds on the theories of human factors engineering, a discipline dedicated to the design of systems and environments for safer, more effective, and more efficient use.

A common finding in all of these studies is that these events occur much more frequently than previously realized. Safety is compromised multiple times per operative procedure so field observations are incredibly rich as a

data source. The landmark paper in this area was published by de Leval and colleagues from the UK in 2000.[4] They showed that 2.8 major and 6.2 minor events compromising safety occurred per case and both major and minor events increased the odds of patient harm. We prospectively observed ten complex general surgery cases to identify factors that influenced safety in the OR.[5] We were able to identify communication breakdown and workload–competing tasks as the two most important factors. By studying the patterns of events surrounding these two areas, we were able to target areas for improvement and design more rigorous studies to further investigate. For example, building on what we learned in the observational study, we performed a more in-depth analysis of the MIMEPS claims data to further understand communication breakdown and develop standards that are currently being implemented to improve communication. Furthermore, we identified the count protocol as a particularly vulnerable part of an operation. We therefore performed a randomized, controlled trial to evaluate whether bar coding sponges could help improve this process.

Conclusion

The OR is the most common site of adverse events and near misses in medicine. It is therefore a high-impact area that should be targeted to improve patient safety. The focus of this work needs to be on understanding system vulnerability and improving resilience. Traditional approaches to research in this area have been outcome-based, often failing to detect recovered events and offering limited information about system factors. Prospective data collection allows for a more accurate estimate of incidence, the identification of contributing factors that can be targeted for intervention, as well as the opportunity to learn about system resilience and provider adaptation. This type of research will improve our ability to learn from adverse events and near misses in the operating room.

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Aviation

Richard C. Karl

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Abstract
Background An increased awareness of the need for safety in medicine in general and in surgery in particular has prompted comparisons between the cockpit and the operating room. These comparisons seem to make sense but tend to be oversimplified.
Discussion Attempts in healthcare to mimic programs that have been credited for the safety of commercial aviation have met with varying results. The risk here is that oversimplified application of an aviation model may result in the abandonment of good ideas in medicine. This paper describes in more depth the differences between medicine and commercial aviation: from the hiring process, through initial operating experience, recurrent training, and the management of emergencies. These programs add up to a cultural difference. Aviation assumes that personnel are subject to mistake making and that systems and culture need to be constructed to catch and mitigate error; medicine is still focused on the perfection of each individual's performance. The implications of these differences are explored.

Keywords Aviation · Healthcare · Safety

Despite an increasing emphasis on safety in healthcare, objective measurement of improvement has been relatively hard to come by. JCAHO data indicate that compliance with such simple tasks such as marking the surgical site and performing a "time out" has actually decreased over the past 4 years.[1] Furthermore, an institution dedicated to safety improvement that launched ambitious crew resource management programs modeled after aviation has reported low compliance rates with these simple tasks after expensive training.[2] Thus, it appears that, though the airlines have become much safer over the past 50 years, it is unlikely that patching their crew resource management training alone onto surgical practice will make us just as safe. To accomplish the level of safety that is predictably achieved by high reliability industries like nuclear power and the airlines, we will need to change our culture.

The good news is that cultural change does not require the purchase of expensive equipment or the discovery of a gene. The unfortunate news is that cultural change, especially in a profession as complex as medicine, is difficult to accomplish. Addressing the Royal College of Physicians, safety expert James Reason said, "Aviation is predicated on the assumption that people screw up. You (healthcare professionals) on the other hand, are extensively educated to get it right and so you don't have a culture where you share readily the notion of error. So, it is something of a big sea change."[3]

The danger is that our frustration with the lack of improvement in safety areas will lead us to abandon techniques than can work if properly understood and applied. A survey of aviation training methods makes it clear that airlines do much more than crew resource management in an effort to be safe. That they are safe is not in dispute. How do they do it? How did they change the culture from the imperious captain/tyrant to cockpit leader with "confident humility?"

Here are some of the ways that airlines instill cultural mores into their operations. It starts at the beginning with personnel selection. The newly hired pilot is in many ways analogous to a new faculty hire just finishing his or her

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R. C. Karl (✉)
University of South Florida Department of Surgery,
12901 Bruce B Downs, MDC Box 16, Tampa, FL 33612, USA
e-mail: karl@moffitt.org

residency. The incoming first officer has at least 2,500 h of flying time and a certain percentage of that is in turbine aircraft as pilot in command. At Southwest Airlines, the new pilot has already obtained a Boeing 737 type rating.

The first noticeable difference is in the hiring methods. Airlines interview prospective pilots in an orderly and scripted manner. They do not have search committees as we know them. Although all pilot applicants must have letters of recommendation, the interview is extremely important. Applicants are asked "about a time when you disagreed with a superior and how did you resolve the conflict?" In the line-oriented interview, applicants are placed in a cardboard cockpit seated next to a captain and in front of a retired captain. A series of problems is provided to the applicant and he or she has 7 min to solve the conundrum. As the clock winds down, those who communicate well with other crew members and accept responsibility as well as input are rated highly. The airlines distinguish between an autocratic "captain of the ship" and a leader. Most surgery departments hire new faculty by letters of recommendation, common training experience or friendships, and an unstructured interview.

Once hired, the new pilot undergoes 8 weeks of training. Issues like the importance of flight operations manual, dress and behavior codes, and practical matters such as how to preflight the airplane, fly the airplane, and manage emergency procedures according to clear company policies are all covered. At the center of this training is the concept of "flow," the sequence of maneuvers, discussions, checklists, and read backs that mark the conduct of a safe flight. At the conclusion, each new hire must pass a simulator check ride or proficiency check. In medicine, we frequently ask the new surgeon to become credentialed by filling out some paper work, give them an office, office hours, and block time in the operating room. Orientation programs are usually regulatory and not culturally oriented.

Once flying the line, new pilots undergo 25 h of Federal Aviation Administration required initial operating experience. Specially trained check airmen are assigned to the new hires and evaluate them for flying ability, problem solving skills, situational awareness, and crew resource management techniques. In our surgery department, very little mentoring of new faculty has been done traditionally.

Recurrent simulator and ground school training is mandatory every 6 months for captains and every year for first officers. New regulations, checklists, and flight operations are covered extensively during a several day period at full pay. A proficiency check is required prior to return to duty. In surgery, we take a written exam every 10 years that is unlike the type of check ride/knowledge testing that occurs in the airlines. Even with new initiatives for maintenance of competency and skills testing, the various types of surgical practice and subspecialties will require much more elaborate simulation and "ground school" than is typically done by the airlines. Checklists are used routinely and habitually by airline personnel and sporadically by surgical workers. In the airlines and military, checklists are viewed as another member of the crew. They are living, evolving instruments. Checklists are not "to do" lists, but just what they claim to be: methodical reminders to be sure that important procedures have been successfully carried out. "Challenge and Response" are the critical construction format of aviation checklists. In areas where some surgical teams use checklists, they are home grown and are not consistent from one hospital to another. Rarely are they constructed in a challenge and response format. Frequently a box is to be checked, inviting misuse of the checklist.

A major cultural difference between aviation and medicine is our perseveration about documentation rather than actually doing things safely. Thus, a nurse is frequently typing during the time out rather than insuring that the information is accurate. No pilot is asked to fill out a form proving that she checked the landing gear position prior to landing. The checklist is there to be certain the wheels are down, not documented to be down.

Briefings are central to safe airline flight. Several, not just one, are routinely done prior to, during, and after a flight. There are first flight of the day briefings, pre-start briefings, taxi briefings, pre-takeoff briefing, approach and landing briefings, and post-flight debriefings. These multiple communication events are short, patterned, and expected. In surgery, we have a moment referred to as "timeout." This word sounds like a break in the action, as if we are unsafe most of the time and take a break to be safe. In aviation, safety is woven into the fabric of flight. Briefings in the pre-op holding area and in the operating room before induction and before incision are critical steps that are not routinely covered by a "timeout."

Once in the operating room, surgeons are expected to deal with various emergencies by memory, whereas most in-flight emergencies are handled by reference to a "Quick Reference Handbook." In this book, one finds the appropriate algorithms to follow for engine fire, generator failure, sudden depressurization, etc. Most operating rooms have no handy reference materials to guide surgeons, nurses, technologists, and anesthesia personnel when something unexpected occurs. The treatment for bradycardia, for example, is highly individualized based on staff experience and knowledge.

Airliners are designed to function with some pieces of equipment inoperative. A "Minimum Equipment List" handbook contains the rules for deciding whether a flight can continue or begin with, say, an auxiliary power unit generator malfunctioning. In surgery, most equipment, supply, and environment decisions are left to the discretion of the surgeon, who may never have contemplated the consequences of starting an operation without blood available until an unusual antibody is detected.

Duty hours for airline pilots are 14 h on duty and 8 h of flying per day. Rest periods between duty hours are strictly proscribed. Random drug and alcohol testing is an industry standard. In surgery, with the exception of the 80-h work week for resident staff, no mandatory rest periods or routine screening for performance impairing substances is in effect.[4] No fault reporting, as described by Dr. Greenberg in the preceding article, is also an important safety tool in aviation. It is administered by NASA, not by the FAA, and has the mechanisms to preserve reporter anonymity. Though many hospitals have reporting systems, most clinicians are unaware of them and infrequently contribute near miss information.

Below 10,000 ft, all airline operations are under "sterile cockpit rules." No discussion other than that pertinent to the safe conduct of the flight is permitted. Compare this to most operating rooms where irrelevant discussions are frequently entertained even during the most critical portion of the procedure. I know from unhappy personal experience that it is during these times that inadvertent mistakes can be committed, sometimes with disastrous consequences.

Though not exhaustive, this list of differences between aviation and surgery provides some context by which to judge our initial attempts to improve safety. We have a lot more to do than crew resource management. Now is a good time to start. All that is required is will. A safer work environment is not just good for patients; it makes the operating room a calmer place, more fun to work in, more efficient and safer for everybody.[5]

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Safety in the OR: Who's in and Who's out?

Debra Sudan

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Keywords Operating room · Safe OR · OR errors · Malpractice lawsuit · Safety issues

According to the Institute of Medicine report, 2% to 4% of hospitalized patients experience an injury as a result of medical management and 7% to 14% die as a result, making errors the eighth leading cause of death in the US.[1] The Harvard Medical Practice Study found that the most common adverse events for all hospitalized patients were related to medication administration (19%), but wound infection and technical complications accounted for 14% and 13%, respectively.[1] As we examine the potential sources for error in the surgical patient, it is clear that a substantial number of individuals (including nurses, physicians, technicians, residents, medical students, nursing students, pharmacists, anesthesiologists, midlevel practitioners, proctors, pharmaceutical or device representatives, pharmacists, and others) care for each patient in the operating room and throughout their hospitalization, each with the potential to make a mistake or error. It is therefore not surprising that the rate of adverse events in hospitalized patients rises approximately 6% per inpatient day.[1] Examination of errors is therefore a key factor in identifying preventable injuries and developing safer hospitals and operating rooms.

Multiple individuals care for a surgical patient; however, due to the multidisciplinary nature of the team, the team may be only loosely connected and the mode with which communication and the transfer of care occurs varies considerably from hospital to hospital and from department to department within a hospital. Lingard et al. described how various types of failures in communication impacts the occurrence of errors; poor timing of the communication was the most common failure (46%) followed by missing or inaccurate crucial information (36%), exclusion of key individuals from the communication or a failure to resolve the issue during the communication.[2] This study further found that more then one third of communication failures led to a measurable adverse effect on the system in terms of inefficiency, increased team tension, waste of resource, delay, patient inconvenience, or procedural error.

Clearly, our colleagues in anesthesia have demonstrated that systematic analysis of adverse events and dissemination of what is learned can dramatically decrease deaths. The death rate for patients undergoing general anesthesia in 1980 was two deaths per 10,000 individuals and after widespread introduction of systematic reviews has dropped to one death in every 200,000–300,000 anesthetic events despite the increased frequency of complex surgeries and the increased rate of older, sicker patients undergoing even standard surgical procedures. This same systematic analysis to examine surgical adverse events is currently needed.

The Joint Commission introduced a mechanism to collect data through root cause analysis of adverse or "sentinel events" in order to examine errors and disseminate the information with the goal of preventing the repetition of such errors (http://www.jointcommission.org/PatientSafety/). Since 1993, over 700 events have been analyzed including

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D. Sudan (✉)
University of Nebraska Medical Center,
983285 Nebraska Med. Ctr.,
Omaha, NE 68198-3285, USA
e-mail: debra.sudan@duke.edu

wrong site surgery, catheter or tubing misconnection, unintended retention of a foreign object, hospital-acquired or treatment-associated infections, transfusion reactions, and surgical fires and the findings have been widely distributed and are accessible on the website (http://www.jointcommission.org/PatientSafety/). Unfortunately, only a small number of the many preventable errors are submitted to the Joint Commission each year. In a large part, this lack of participation stems from concerns that disclosure of such events may increase the likelihood of malpractice lawsuits and that the information disclosed is not protected from discovery.

Errors in the operating room appear to occur commonly at an average of 9.9 minor errors per operation.[3] Furthermore, an increase in the number of minor errors leads to a higher risk for serious events and an increase in operative time (10 min for every increase of three errors per case). An additional important finding of this study was that experienced teams have decreased rates of minor errors and an improved capacity to recover without escalation to serious events. Operating room errors have been further categorized as either technical or procedural with a mean rate of 1.7 vs. 8.5 per operation, respectively.[4] Procedural errors are more common overall, but operative cases that require use of more complex technology and equipment are associated with increased rates of technical errors. For example, the rate of technical errors per case was 2.68 for laparoscopic cholecystectomy compared to 0.68 for carotid endarterectomy.

Distractions and interruptions appear to be two factors that contribute to the occurrence of errors.[5] Resident experience has also been suggested to have a role in preventable errors and injuries.[6] An additional potential contributor to the occurrence of error is fatigue. Fatigue-related errors has been the impetus for limitations in resident work hours, although few studies have quantified the impact fatigue has on the occurrence of errors or performance in a rigorous fashion. Leff and colleagues measured performance of laparoscopic skills of residents on sequential nights on call and found the first night to be associated with maximal deterioration in performance and subsequent night shifts associated with increased performance toward baseline.[7] Further investigation into contributory factors to the occurrence of errors and mechanisms for adaptation and recovery will likely help to improve safety in the future.

Who should then be in our operating rooms? For the answer to this question, we can look to the published literature noted above and as summarized in the manuscripts by Drs. Greenberg, Karl, and Moorman as well as common sense. The operating room personnel (surgeons, nurses, anesthetists, residents, students, and midlevel practitioners) should be free from excessive fatigue, present in adequate numbers to complete all necessary tasks without excessive stress, experienced individually and familiar with the type of surgery being performed, and have minimal demands on their time and attention by events outside the operating room. The team caring for the patient should have experience working together, be fully trained, and be given responsibility commensurate with their training. These individuals should furthermore be aware of the best evidence-based practices and the most advanced technology available. All aspects of the surgery or new technology should have been previously thoroughly tested and equipment that is properly functioning and for which the entire team has been fully trained should be utilized. Information technology systems should likewise be available that can provide key patient information relevant to the operation, collect data to be utilized in quality improvement, and provide reference information to assist with provision of the right medications, right doses, right route of administration, and right timing of the dose. While this list is rather idealistic, each operating room has limitations in budget and infrastructure which impact to what extent these ideal staffing and equipment needs are feasible. Increased levels of staffing and experience are correlated with increased salary and training costs a difficult issue for hospitals that are dealing with decreasing reimbursement.

Who should be kept out of our operating rooms? Again, we can look to the published literature and common sense. Any individual that is not appropriately licensed and/or credentialed (as defined by hospital policy and determined by the credentialing office) clearly should not be allowed entry into the operating room to participate in patient care. In addition, disruptive physician behavior has been shown to adversely affect nursing morale and contribute to increased staff turnover and decreased teamwork.[8] Likewise, distractions and interruptions should be minimized for all members of the team in order to allow for concentration on the surgical procedure. Finally, complex multistep tasks with a high degree of reliance on memory and diligence should be replaced with checklists, reminders, and redundancy in processes.

Clearly, investigation into the causes of preventable errors and the appropriate solutions has provided some insight into how we may provide safer health care in our operating rooms and in our hospitals in general. Organizing our staff and equipment to maximize experience, increase redundancy in areas of safety concerns, and provide simplistic technological designs will assist in movements toward a safer operating room. There remains a tremendous opportunity to further examine safety issues and to identify

solutions. We hope this symposium will provide a bit of the roadmap toward that end.

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Building Better Teams in Surgery

Donald W. Moorman

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Abstract This manuscript represents an overview of a presentation at the SSAT 49th annual meeting which describes the evolution of the author's work within surgery to build and advance teamwork into processes of care.

Keywords Surgery · Team-based practice program · Interdisciplinary teamwork

Introduction

Surgical care has the time-honored paradigm of individual performance at perfection. Thus, not surprisingly, the surgeon's craft has been characterized as one where individual skill, judgment, and performance are the critical determinants of outcome. This paradigm has been sustained by the notion of the "super surgeon" and is personified in many of our surgical heroes today. However, a Harvard medical error study revealed that errors frequently occur and impact patients. Also evident was that individual performance failures in systems relying on this paradigm often manifest with patient harm.[1] The Institute of Medicine analysis of medical errors published in 1999 corroborated this observation, leading to the recommendation that healthcare systems should develop and implement programs to train and utilize team-based practice in their organizations.[2]

Beth Israel Medical Center and New England Deaconess Hospital, two major Harvard teaching hospitals, were merged in 1996. Existing systems of effectiveness were thereby disrupted, allowing for evolution to new systems of care. In response to this cultural disruption, an interdisciplinary team of leaders in surgery, anesthesia, and nursing services were able to study the impact of the disruption on staff efficiency and morale, craft a set of early goals for a team training program, then develop and implement the training internally. Through the evolution of this opportunity, the team has realized that team-based practice can only be implemented through didactic education (a teamwork tool kit), ongoing practice with those tools, and integration of the concepts into daily workflow.

The didactic presentation was developed as an adaptation of the didactic module of the Department of Defense sponsored BIDMC Labor and Delivery team training study.[3] As two members of the steering committee were simultaneously immersed in a patient safety fellowship, the program was further enhanced with tools gathered in the fellowship, as well as other concepts derived from the current literature. For example, because many of the employees had expressed concerns regarding their potential for disciplinary action when speaking to or holding the line across the perceived professional hierarchy, significant time was dedicated to the concepts of a just culture. The program contained five modules focusing on: team concepts, communication, error science including the recognition of the conditions of failure, cross-monitoring, and personal self-governance, especially around task

This paper was originally presented as part of the SSAT Education Committee Panel on Teaching Safety in the OR at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA, USA. The other articles presented in the panel were Jones DB, Teaching Safety in the OR; Greenberg CC, Learning from Adverse Events and Near Misses; Karl RC, Aviation; and Sudan DL, Safety in the OR: Who's In and Who's Out?

D. W. Moorman (✉)
Department of Surgery, Beth Israel Deaconess Medical Center,
110 Francis Street, Suite 9B,
Boston, MA 02215, USA
e-mail: dmoorman@bidmc.harvard.edu

saturation and fatigue management. The training was conducted on-site in small interdisciplinary groups with a 4-h contact time.

Reiterative practice must be facilitated through daily use of the tools and efforts to use the team concepts to solve problems encountered in work. Upon completion of the didactic training, the physicians and staff were encouraged to experiment with the tools. This practice was facilitated through the introduction of briefings and the implementation of white boards in the OR's, which identify team members and enhance transfer and display of critical patient information. Techniques of tension recognition and conflict resolution were also introduced in the didactic module, and a conflict resolution pathway has been created to complement tension management. This has virtually eliminated disruptive events. All disciplines were encouraged to practice with the skills and pull in participation of others in the immediate OR team. Posters displayed in each of the operating rooms outlining communication checklists were the structure around which team-based communication was encouraged.

Additionally, as we had access to a high-fidelity simulation center, whole-team simulations were developed for some OR working groups, such as minimally invasive surgery. These scenarios allow teams to work in the conduct of an operation and personally review their individual and the team's performance in video debriefing. One such scenario was utilized to demonstrate the ability to differentiate experts from novices in both technical responses to crisis and team decision-making behaviors.[4]

As the *team-based practice* program evolved from our initial efforts at team training, the steering group became aware of opportunities to introduce structured teamwork processes. Introduction of structure was done to increase adoption of the teamwork tools. The steering group progressively introduced checklists and other tools, which embedded interdisciplinary accountability while documenting appropriate care processes. An example is the introduction of a checklist in the holding area to highlight critical preoperative information, which also documented that the necessary disciplines had reviewed this information. Communication and acknowledgement by the team was enhanced as individual team members signed off on the process document. More recently, we have introduced a novel concept: intraoperative pathways, which have been submitted for separate publication.[5] These pathways standardize, segment, and create checklist prompts for each segmented phase of a complex operation. Included within the pathway are the communication and process of care prompts, allowing more uniform accomplishment of care processes throughout the case. Each phase has documentation to allow not only call out of variance but also opportunity for resolution at the completion of the case. Resolution of the documented variances facilitates recognition of opportunities to further refine the pathway. Significant efficiencies and cost reductions have been realized. Importantly, because the pathway was created and is maintained by a mutually involved interdisciplinary team, acceptance in use has been high, and staff surveys recognize the pathways facilitating their efficiency and team communication.

In conclusion, the work presented in this session is an overview of a performance improvement journey within our surgical care community at the Beth Israel Deaconess Medical Center. Our efforts to integrate interdisciplinary teamwork into routine work through structured communication and action prompts have yielded significant improvements. We have demonstrated that interdisciplinary teamwork, monitoring, and accountability can be integrated into the practice tools. Early indicators of success have shown many of the desired goals have been achieved. However, the team recognizes that the impact would likely not have occurred if all three goals had not been implemented. Most of the metrics of the program realized improvement, some to the pre-project goals, and the participants had a measured improvement in a safety culture survey, which was sustained through 18 months, as will be reported elsewhere. Staff retention in the operating rooms has significantly improved, manifesting the improved environment of care.

One obvious flaw of this report is that, in fact, there is no control; rather, this is an observation. One might argue that this is an impact of leadership rather than implementation and evolution of this program. To that question, the program has been implemented in other medical centers with varied demographics at this point, and experiences observed will be forthcoming.

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An Improved Method of Assessing Esophageal Emptying Using the Timed Barium Study Following Surgical Myotomy for Achalasia

Arzu Oezcelik · Jeffrey A. Hagen · James M. Halls · Jessica M. Leers · Emmanuele Abate · Shahin Ayazi · Joerg Zehetner · Steven R. DeMeester · Farzaneh Banki · John C. Lipham · Tom R. DeMeester

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Abstract
Introduction The timed barium study (TBS) is used to assess esophageal emptying in patients with achalasia. Improvement in emptying correlates with outcome after endoscopic therapy, but the results of the TBS have been variable after myotomy. Our aim was to evaluate a new method for assessing improvement in emptying after myotomy.
Methods A TBS was performed before and 3–6 months after myotomy in 30 patients. Emptying was assessed by measuring the percent difference in area of the barium column on films obtained 1 and 5 min after ingesting 150 ml of barium. Initial esophageal clearance was also assessed by comparing the area of the barium column on 1-min images obtained before and after therapy. Both measures were compared to clinical outcome.
Results After myotomy, 21 patients (70%) had no symptoms, four (13%) had mild, and five (17%) had moderate/severe symptoms. Using the standard method, esophageal emptying before and after surgery were not significantly different (25% vs. 37%; $p=0.22$) and did not correlate with clinical outcome. In contrast, initial esophageal clearance improved significantly (median 81%) and correlated with clinical outcome.
Conclusion Esophageal emptying measured by the standard method is not useful to assess outcome after myotomy. However, initial esophageal clearance correlates well with clinical outcome.

Keywords Achalasia · Timed barium study · Heller myotomy · Esophageal emptying

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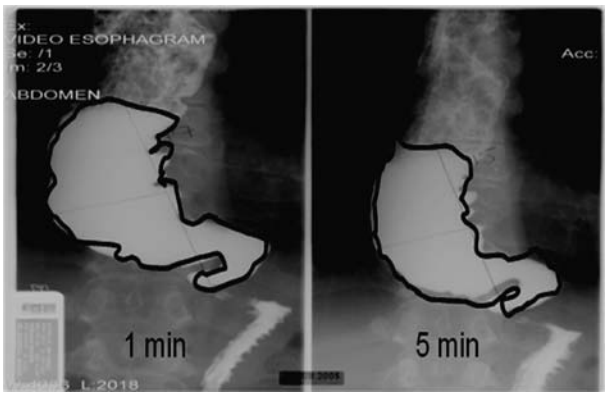
A. Oezcelik · J. A. Hagen (✉) · J. M. Leers · E. Abate · S. Ayazi · J. Zehetner · S. R. DeMeester · F. Banki · J. C. Lipham · T. R. DeMeester
Department of Surgery, University of Southern California, Keck School of Medicine,
1510 San Pablo Street,
Los Angeles, CA 90033, USA
e-mail: hagen@surgery.usc.edu

J. M. Halls
Department of Radiology, University of Southern California, Keck School of Medicine,
Los Angeles, CA 90033, USA

Introduction

Achalasia is an esophageal motility disorder with a prevalence of less than 0.001% in the United States.[1] It is an immune-mediated destruction of the esophageal myenteric plexus of unknown etiology.[2] Treatment options include Heller myotomy, pneumatic dilatation, and botulinum toxin injection. In recent years, the laparoscopic Heller myotomy with partial fundoplication has emerged as the procedure of choice for long-term palliation of achalasia.[3, 4] The goal of the therapy for achalasia is to improve esophageal emptying while avoiding troublesome reflux.[4]

The timed barium study (TBS) has been described as an objective method to assess esophageal clearance in patients with achalasia. The test is performed by having the patient drink a known volume of barium followed by fluoroscopy images obtained at 1 and 5 min after ingestion. In untreated patients with achalasia, there is typically minimal emptying



$$\text{Esophageal Emptying} = \frac{\text{area 1 min} - \text{area 5 min}}{\text{area 1 min}} \times 100$$

Figure 1 Esophageal emptying as calculated using the standard method. The area of the barium column on the 5-min spot film is compared to the area on the 1-min film using the formula shown.

between the two images. Timed barium studies done before and after pneumatic dilatation have shown improved emptying.[5] Results of the TBS have been more variable after surgical myotomy.[6] In this situation, there is often dramatic improvement in initial passage of the barium into the stomach as that there is minimal residual barium in the esophagus on the 1-min image. Consequently, when the 1-min images are compared with the 5-min images, there is little additional emptying, making the calculation of esophageal emptying by the standard method less reliable.

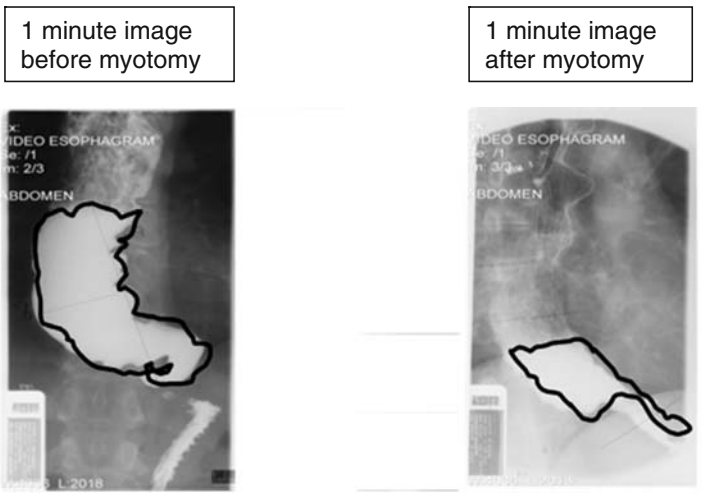
The aim of this study was to evaluate a new method to analyze the TBS before and after surgical myotomy for achalasia.

Materials and Methods

Between 1999 and 2007, 122 patients underwent Heller myotomy for achalasia at the University of Southern California. All patients underwent upper gastrointestinal endoscopy and esophageal manometry. Only patients who had a TBS before and 3–6 months after surgical myotomy were included in the study. Clinical symptoms were assessed at the same time interval, and symptoms were graded on a scale from 1–3 (1=none; 2=mild; 3=moderate/severe).

The TBS was performed in the Department of Radiology at the University of Southern California using a standard protocol. The study was done with the patient in the upright position using a fixed fluoroscopy unit with an image intensifier in the 15-in. mode. The patient was instructed to drink 150 ml of barium as quickly as comfortable within a time interval of 30–45 s. Spot films of the esophagus were taken 1 and 5 min after ingestion of the barium.[5] The area of the barium column was measured on timed digital images. Esophageal emptying was calculated by comparing the area of the residual barium column on the 1- and 5-min images (Fig. 1). Improvement in esophageal emptying was determined according to the standard published method by comparing the percent emptying preoperatively to that measured postoperatively.

We also assessed initial esophageal clearance by comparing the area of the barium column on the 1-min images obtained before and after myotomy (Fig. 2). We classified initial esophageal clearance of 100–71% as excellent, 70–41% as good, and 40–0% as poor clearance. Esophageal emptying, as measured by the standard method and by the initial esophageal clearance method, was compared with



$$\text{Initial Esophageal Clearance} \frac{\text{area 1 min premyotomy} - \text{area 1 min postmyotomy}}{\text{area 1 min premyotomy}} \times 100$$

Figure 2 Initial esophageal clearance calculated by comparing the area of the barium column on the 1-min spot films taken before and after surgical myotomy using the formula shown.

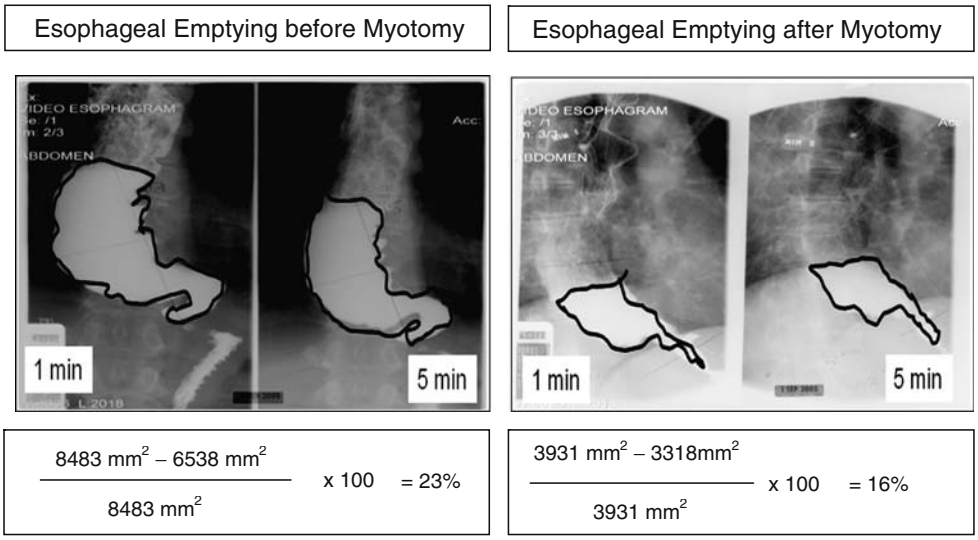


Figure 3 Esophageal emptying before and after surgical myotomy calculated using the standard method in a typical patient. The difference in emptying (24% vs. 16%) is minimal.

clinical outcome. The study was approved by the Institution Review Board of the University of Southern California.

Continuous variables are reported as median and 25th and 75th percentiles. A paired *t* test was used to compare esophageal emptying before and after myotomy and to compare the area of barium column at 1 min before and after myotomy. Fisher's exact test was used to compare clinical outcome and the results of the TBS. A *p* value of less than 0.05 was considered statistically significant.

Results

There were 30 patients treated by laparoscopic myotomy and partial fundoplication who had a TBS before and 3–6 months after operation. The study cohort included 19 male and 11 female patients with a median age of 50 years (IQR 41–59). All 30 patients (100%) presented with dysphagia, 28 (93%) also experienced regurgitation, and 20 (67%) had chest pain. Five patients (17%) had a failed previous endoscopic dilatation, and three patients (10%) had failed Botox® injection.

At clinical follow-up 3–6 months after myotomy, 21 patients (70%) had no symptoms, four (13%) had mild dysphagia, and five (17%) had moderate/severe dysphagia. Regurgitation and chest pain were relieved in all patients.

The results of the TBS in a typical patient are show in Fig. 3. Using the standard method, little difference in emptying is evident. Figure 4 shows the results of the TBS

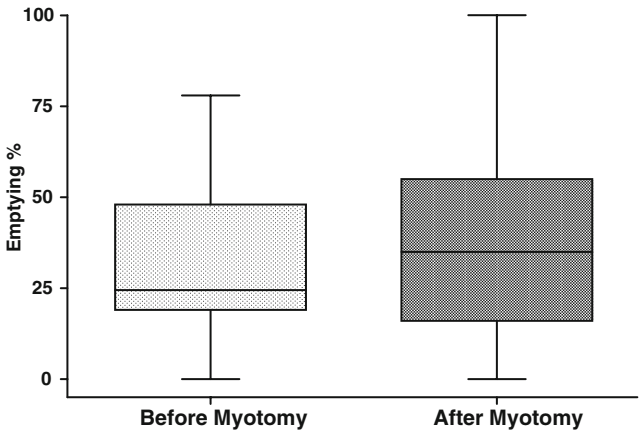


Figure 4 Results of the timed barium study in 30 patients using the standard calculation. There was no significant difference in emptying (25% vs. 37%, $p=0.22$).

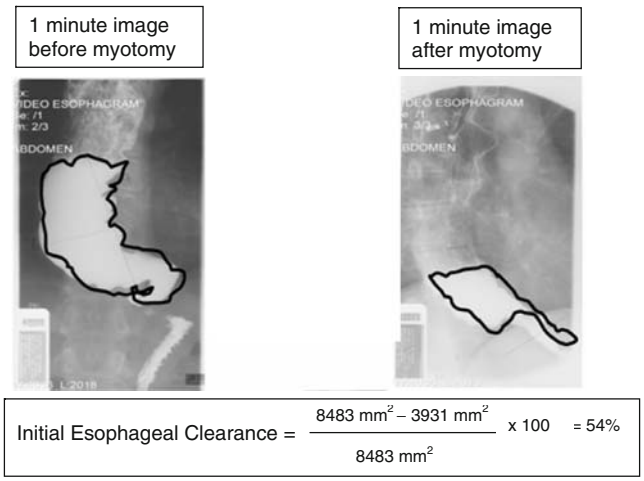


Figure 5 The calculation of initial esophageal clearance before and after surgical myotomy in the patient whose timed barium study calculated by the standard method is shown in Fig. 3. A significant improvement in initial esophageal clearance after surgical myotomy is noted.

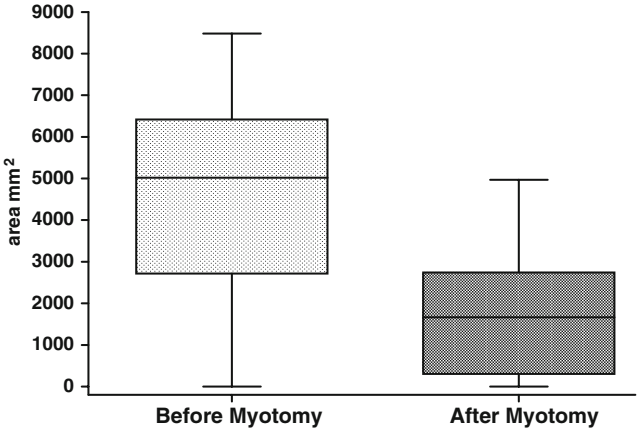


Figure 6 Results of the timed barium study in 30 patients using the initial esophageal clearance calculation. Initial esophageal clearance was significantly improved after myotomy (p=0.0001).

in all patients using the standard method. There was no significant difference in emptying (25% vs. 37%, p=0.22).

The method of evaluating the TBS by calculating the initial esophageal clearance in a typical patient is shown in Fig. 5. The area of the barium column on the 1-min spot film after surgical myotomy was significantly smaller than the preoperative study. The results in all 30 patients are shown in Fig. 6. The initial esophageal clearance calculation above showed a significant improvement in median clearance after surgical myotomy of 81%. Excellent clearance was seen in 15 patients (50%), good clearance in 11 (37%), and poor clearance in four (13%). The relationship between improvement in initial esophageal clearance and clinical outcome is shown in Fig. 7. Patients with good or excellent clearance were significantly more likely to be asymptomatic, whereas all patients with poor clearance had moderate/severe persistent dysphagia.

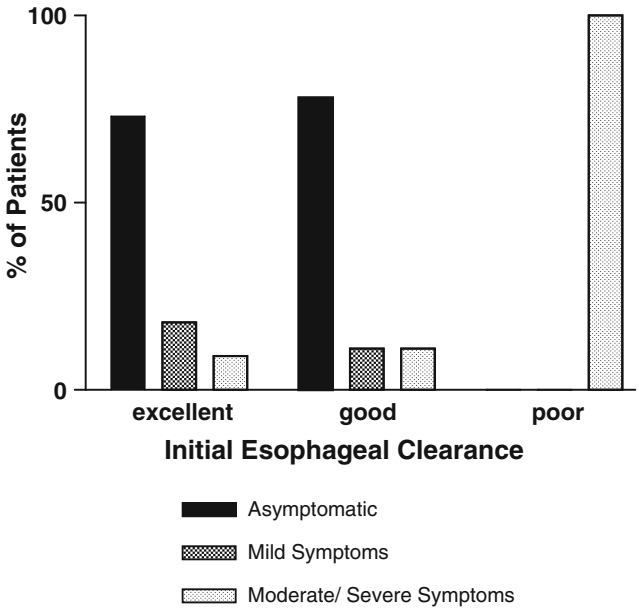


Figure 7 Comparison of initial esophageal clearance and clinical outcome after surgical myotomy.

Table 1 shows the association between the degree of clinical symptoms and the outcome of the TBS calculated using the standard method and the method of initial esophageal clearance. There was no association between clinical symptoms and the standard TBS. In contrast, improvement in initial esophageal clearance correlated well with clinical outcome.

Discussion

The goal of therapy in achalasia is to reduce outflow resistance at the LES in order to improve esophageal emptying. Success can be evaluated based on clinical symptoms or measuring the clearance of barium from the esophagus using upper gastrointestinal radiographic imaging studies. Clinical symptoms have been found to be unreliable in assessing the success of therapy since achalasia patients often have a charmed deception with any therapy and express dramatic clinical benefit from small degrees of improved emptying.[7–9]

The TBS has been described as an objective test to assess esophageal emptying. The test was initially used to assess improvement in emptying in patients who underwent pneumatic dilatation or botulinum toxin injection.[5] When the TBS was used to assess response to surgical myotomy, there was disparity between clinical outcome and the change in esophageal emptying.

A major shortcoming of the standard method for calculating improved emptying on the TBS is that it does not account for a change in the initial volume of barium that passes directly into the stomach. As a result, improvement in this initial emptying of the esophagus is missed on the standard TBS. In clinical practice, we have observed a dramatic difference in the area of the barium column on the

Table 1 Association Between Clinical Symptoms and Results of the TBS Calculated by the Standard Method and Initial Esophageal Clearance

	No symptoms (n=21)	Mild symptoms (n=4)	Moderate/ severe symptoms (n=5)	Kruskal–Wallis p value
Standard method (ratio of emptying pre- vs. post-therapy)	0.7 (0.2–1.6)	0.4 (0.2–2.7)	0.9 (0.6–1.8)	0.78
Initial esophageal clearance (percent improvement)	89 (77–98)	61 (48–71)	44 (28–45)	<0.0002

1-min images taken before and after surgical myotomy in a number of patients. This led us to evaluate a new method for assessing improvement in esophageal emptying after surgical therapy for achalasia, which we defined as initial esophageal clearance.

Our results have confirmed previous observations that clinical outcome after myotomy does not correlate with improved emptying on the TBS when the standard method of calculation is used. Further, we have shown that initial esophageal clearance is significantly improved following myotomy and that the degree of improvement correlates with clinical outcome. This suggests that calculating initial esophageal clearance is a better way to assess response to surgical therapy. A less than 40% improvement in initial esophageal clearance indicates that moderate to severe dysphagia will usually persist.

It is likely that the initial esophageal clearance calculation of the TBS would also predict the success of non-surgical therapy. Our therapeutic approach in patients with achalasia is primarily a surgical myotomy. Consequently, we do not have sufficient patient data after pneumatic dilatation or botulinum toxin injection to assess the calculation of initial esophageal clearance after these types of therapy. Hopefully, future studies will address this issue.

Conclusion

Improvement in emptying, as traditionally measured by a timed barium study, is not a reliable way to assess outcome after surgical myotomy for achalasia. A new method of measuring emptying, defined as initial esophageal clearance demonstrates significant improvement after surgical myotomy, which correlates with clinical outcome.

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Comparison of Surgically Resected Polypoid Lesions of the Gallbladder to their Pre-operative Ultrasound Characteristics

Martin D. Zielinski · Thomas D. Atwell · Peyton W. Davis · Michael L. Kendrick · Florencia G. Que

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Abstract
Background Polypoid lesions of the gallbladder (PLG) have been a common finding on ultrasound examinations of the abdomen and are more prevalent since our use of equipment incorporating pulse shaping increased bandwidth, and enhanced phase use for image reconstruction began in 1996. Our study correlates the pre-operative ultrasonographic findings of these lesions to the surgically resected specimen with specific regard to identifying neoplastic polyps.
Methods A retrospective review was performed of 130 patients who had a pre-operative ultrasound of the gallbladder and subsequently underwent cholecystectomy between August 1996 and July 2007 at the Mayo Clinic Rochester.
Results Seventy-nine pseudopolyps (cholesterol polyps, inflammatory polyps, and adenomyomas) and 15 neoplastic polyps were identified on histopathologic analysis. However, 36 patients (27%) did not have a PLG upon histopathologic analysis. Thirty-one polyps had suspicious ultrasonographic characteristics for neoplastic changes. Twenty-nine were ≥10 mm, 12 had vascularity, and one demonstrated invasion. Of these, there were 23 pseudopolyps and six true polyps with neoplastic changes on final pathology (four dysplastic adenomas and two adenocarcinomas). Three asymptomatic polyps ≤10 mm (4%) in maximum diameter based on pre-operative ultrasound imaging (US) had neoplastic changes at pathology (two dysplastic adenomas and one adenocarcinoma). Several statistically significant risk factors were identified that increased the likelihood for malignancy in a PLG: history of primary sclerosing cholangitis (PSC), local invasion, vascularity, and ≥6 mm maximum diameter based on pre-operative US. Of PLGs ≤10 mm, 7.4% were neoplastic. Twenty-five patients were followed up with at least two serial ultrasound examinations. Of these, seven demonstrated polyp growth. None of these specimens demonstrated neoplastic changes. The positive predictive value (PPV) and negative predictive value (NPV) for ultrasound diagnosing neoplastic changes based on current criteria was 28.5% and 93.1%, respectively, with a false negative rate of 5.0%. Expanding the criteria to include cholecystectomy for PLGs≥6 mm changes the positive predictive value and negative predictive value to 18.5% and 100%, respectively, with a false negative rate of 0%.
Conclusion Histopathologic analysis of polypoid lesions of the gallbladder continues to be the gold standard to identify malignancy. Ultrasound has been used extensively in the pre-operative management of these lesions, but modern ultrasound techniques are unable to differentiate between benign and malignant PLGs with any certainty. We recommend that strong consideration be given to surgical resection of PLGs≥6 mm based on pre-operative US due to the significant risk of neoplasm. Additionally, PLGs in all patients with PSC, any patient in whom diligent long-term follow-up cannot be completed, and lesions that demonstrate growth, vascularity, invasion, or are symptomatic require cholecystectomy.

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M. D. Zielinski (✉) · P. W. Davis · M. L. Kendrick · F. G. Que
Department of Gastrointestinal and General Surgery, Mayo Clinic,
200 1st St SW, Rochester, MN 55905, USA
e-mail: Zielinski.martin@mayo.edu

T. D. Atwell
Department of Radiology,
Mayo Clinic,
Rochester, MN, USA

Keywords Polyps · Gallbladder · Ultrasound · Adenocarcinoma · Adenoma to carcinoma sequence

Introduction

Gallbladder adenocarcinoma, responsible for 6,500 annual deaths, is the most common malignancy to arise from the biliary tract and carries a dismal prognosis once an advanced stage has been reached.[1–4] Early diagnosis and treatment in the form of cholecystectomy may reduce mortality.[5] Gallbladder cancer is thought to arise from adenomas that undergo malignant transformation based on the adenoma to adenocarcinoma sequence.[6,7] Kozuka et al. demonstrated a size-dependent risk of cancer in their analysis of 1,605 gallbladder specimens.[6] All gallbladder adenomas with a foci of adenocarcinoma were 12 mm in diameter or greater, while all benign adenomas were 12 mm or smaller. Their recommendation, therefore, was cholecystectomy for all polyps greater than 10 mm based on pre-operative ultrasound characteristics to allow for error. This criterion has become the standard of care for gallbladder polyp resection in regards to size.

Polypoid lesions of the gallbladder (PLG), defined as an elevation of the gallbladder mucosa, can be described by two broad categories: true polyps and pseudopolyps. True polyps demonstrate neoplastic changes but can be benign, but potentially pre-malignant, adenomas in addition to dysplastic adenomas (both low and high grade) and adenocarcinomas. Pseudopolyps are characterized by benign lesions, such as cholesterol polyps, inflammatory polyps, and adenomyoma. As ultrasound technology has improved, the detection of PLGs has increased and can be found in 5% of adults.[5,8] Unfortunately, ultrasound has been unable to accurately differentiate between benign, pre-malignant, and malignant lesions.[9,10] Studies with endoscopic ultrasound (EUS) and contrast-enhanced ultrasound have been performed to further differentiate the lesions that require removal. However, there are little data to support the accuracy of this approach. Though higher resolution has led superior rates of diagnosis, significant uncertainty remains in the ability to differentiate benign from malignant lesions.[11–14]

The ultrasonographic equipment at our institution was upgraded in 1996 with the abilities to incorporate pulse shaping, increased bandwidth, and enhanced phase use for image reconstruction. This study reports our experience with pre-operative ultrasound characteristics of PLG and correlates their histopathological findings.

Materials and Methods

Institutional review board authorization was obtained to retrospectively review data on 130 patients (85 women and 45 men) that had a pre-operative ultrasound examination of the gallbladder and subsequently underwent cholecystectomy between August 1996 and July 2007 at our institution. These included laparoscopic and open cholecystectomies in addition to patients undergoing exploration for other disease processes. Patients with known adenocarcinoma of the gallbladder were excluded. One hundred three (79%) patients had pre-operative US studies available for re-review by the contributing staff radiologist. If the original films were unavailable, the original radiology report was used. Histopathologic analysis was based on the original pathology reports. Neoplastic lesions were defined as benign adenomas, dysplastic adenomas, and adenocarcinomas. The remaining pseudopolyps were non-neoplastic.

In 1996, our radiology department upgraded to Acuson Sequioa ultrasound systems (Siemens Medical Solutions, Mountain View, CA, USA). This change provided increased system sensitivity by decreasing image noise. In addition, the upgrade incorporated the use of phase information for more accurate image reconstruction. Subjectively, it was felt that these changes resulted in increased conspicuity of very small abnormalities in the gallbladder.

Continuous variables were analyzed by the Student *t* test. Bivariate analysis of categorical variables was performed using the Pearson's chi-squared test or Fisher's exact test. Statistical significance was determined by a P value<0.05.

Results

Seventy-nine pseudopolyps (cholesterol polyps, inflammatory polyps, and adenomyomas) and 15 true polyps were identified on histopathologic analysis (Table 1). However, 36 patients (27%) did not have a PLG upon histopathologic analysis. The pre-operative ultrasonographic characteristics of all PLGs are listed in Table 1, along with the pertinent history. Based on pre-operative US, 31 PLGs had traits worrisome for malignancy, and the remaining were thought to be benign. Of the PLGs with concern for neoplasia, 29 had a maximum diameter greater than or equal to 10 mm, 12 demonstrated vascularity, and one invaded into the liver. Of these, eight had neoplastic changes on histopathological diagnosis: two with benign adenomas, two with low-grade dysplasia, two with high-grade dysplasia, and two with adenocarcinomas. Of the PLGs thought to be benign, seven had neoplastic changes: four benign adenomas, two dysplastic adenomas, and an adenocarcinoma. In total, therefore, there were 15 PLGs with neoplasia (Table 2). We identified four ultrasonographic

Table 1 Features of Benign vs. Malignant PLG

	Histopathologic characteristics						*P* value
	Total (*n*=130)	No polyp (*n*=36)	Pseudopolyp (*n*=79)	True polyps			
				Benign adenoma (*n*=6)	Dysplastic adenoma (*n*=6)	Adenocarcinoma (*n*=3)	
Sex							
Male	45	8	30	1	3	3	0.2002
Female	85	28	49	5	3	0	
Age							
<60	92	23	59	5	3	2	0.5723
≥60	38	13	20	1	3	1	
PSC							
Yes	7	2	2	1	1	1	0.0049
No	123	34	77	5	5	2	
Symptoms							
Yes	93	31	54	3	3	2	0.2063
No	37	5	25	3	3	1	
US diameter (mm)							
1–5	35	13	22	0	0	0	0.0075
≥6	64	13	40	4	5	3	0.0115
≥10	29	2	18	3	4	2	0
Invasion							
Yes	1	0	0	0	0	1	0.01
No	114	27	62	4	5	2	
Vascularity							
Yes	12	1	5	1	3	2	<0.0001
No	89	26	57	3	2	1	
# polyps							
Single	56	16	29	4	5	2	0.0521
Multiple	52	16	33	2	0	1	
Cholelithiasis							
Yes	28	10	15	0	2	1	0.8150
No	88	22	55	6	3	2	
Shape							
Sessile	15	3	8	3	0	1	0.6013
Pedunculated	81	23	51	0	5	2	

characteristics that were statistically significant risk factors for the presence of a neoplasia: size equal to or greater than 6 mm in maximum diameter, a single polyp, vascularity, and liver invasion. Age and cholelithiasis were not statistically significant risk factors.

There were 82 patients (63%) that had discrepancies between the pre-operative US and the post-operative analysis of the gallbladder specimen. The majority of the inconsistencies were regarding the presence of a PLG. One hundred twenty-one patients were diagnosed with a PLG based on the pre-operative US, and nine patients were diagnosed only on gross specimen analysis. Thirty-six patients (27%) did not have a PLG upon histopathologic analysis. Two of these were thought to be greater than 10 mm pre-operatively. Additionally, numerous examples of size discrepancy were present. Twenty-nine PLG (22%) diameters were overestimated by more than 4 mm, while eight (6%) were underestimated by the same amount.

Twenty-five patients were followed up with at least two serial ultrasound examinations. Of these, nine demonstrated polyp growth. Four of these lesions were associated with neoplasia. One of the PLGs followed up by serial US demonstrated no growth, but was positive for a dysplastic adenoma.

The most common indication for cholecystectomy were symptoms or pathology attributed to the gallbladder, including cholelithiasis, cholecystitis, and gallstone pancreatitis. Forty (30%) patients underwent cholecystectomy due to concerns directly related to the PLG, including diameter ≥10 mm, PLG growth, and a history of PSC. Ten patients underwent incidental cholecystectomy during concurrent hepatic resection, liver transplant, and pancreatic surgery.

Table 2 Summary of Neoplastic PLGs

Age/sex	PSC	Indication for US	US findings		Histopathologic analysis	
			Size (mm)	Neoplastic features	Size (mm)	Pathology
66M	Yes	PSC	6	None	10	Two dysplastic adenomas (LGD)
77F	No	Rectal cancer	<10	None	7	Single dysplastic adenoma (HGD)
46F	No	RUQ pain	18	Size≥10 mm	20	Single adenoma (LGD)
55M	Yes	PSC	8	Size≥10 mm	18	Adenocarcinoma
56M	No	Rectal cancer	22	Size≥10 mm, vascular	20	Single dysplastic adenoma (LGD)
62F	No	RUQ pain	33	Size≥10 mm	20	Two dysplastic adenomas(HGD)
60M	No	Jaundice	23	Size≥10 mm, vascular	25	Single dysplastic adenoma (HGD)
62M	No	RUQ pain	31	Size≥10 mm	45	Adenocarcinoma
53M	No	RUQ pain	36	Size≥10 mm, vascular, invasion	53	Adenocarcinoma
59F	No	RUQ pain	6	None	4	Multiple benign adenomas
41F	No	RUQ pain		None		Benign adenoma
58F	No	Hepatic adenoma		None	4	Benign adenoma
44F	No	RUQ pain	8	None	6	Benign adenoma
66F	No	RUQ pain	10	Size, vascularity		Benign adenoma
32M	Yes	PSC	15	Size	8	Benign adenoma

Seven patients had a history of PSC, two of which had neoplasia (dysplastic adenoma and an adenocarcinoma). The remaining four patients with PSC had benign PLG that measured 7 mm or greater on pre-operative US.

Mean follow-up was 32 months. There were five deaths within the cohort, none of which were related to the procedure or gallbladder adenocarcinoma. The mortality in the neoplasia group was 6.7% (one of 15). The cause of death was widely metastatic rectal adenocarcinoma. When laparoscopic or open cholecystectomy was performed in the absence of other procedures, the total morbidity was 0.8%. There were no bile duct injuries.

The positive predictive value and negative predictive value for ultrasound diagnosing a neoplastic PLG based on current criteria was 28.5% and 93.1%, respectively, with a false negative rate of 5.0%. With the criteria expanded to include cholecystectomy for PLGs≥6 mm, the positive predictive value and negative predictive value change to 18.5% and 100%, respectively, with a false negative rate of 0%. (Table 3)

Table 3 Statistical Analysis

	Pre-operative US diameter	
	≥10 mm (%)	≥6 mm (%)
Sensitivity	66.7	100
Specificity	79.1	43.8
PPV	20.7	11.9
NPV	96.6	100
False negative rate	2.5	0

Discussion

Histopathologic analysis is the gold standard in diagnosing benign and neoplastic polyps that arise from the gallbladder. The difficulty arises in that cholecystectomy is required. Kozuka et al. demonstrated a distinct cutoff point between benign and malignant lesions at 12 mm based on the analysis of resected gallbladder specimens. Their recommendation therefore was cholecystectomy for PLG greater than 10 mm. Koga et al. found that only 3.2% of PLGs less than 10 mm in diameter were neoplastic but that the remaining majority were benign and therefore restated the recommendation for cholecystectomy for PLG greater than 10 mm. These papers and others were based on gross specimen analysis. Correlation of the PLGs to their respective pre-operative US diameter was not performed despite their recommendations.[6,15,16]

Multiple noninvasive modalities, including ultrasound and endoscopic ultrasound, have been extensively studied in order to differentiate non-neoplastic from neoplastic PLGs pre-operatively. Kubota et al. analyzed 72 gallbladder specimens to their pre-operative ultrasound characteristics.[17] Twenty-two percent of neoplastic PLGs were less than 10 mm. They were able to correlate other authors findings that most (56%) neoplastic polyps were sessile based on the pre-op US classification, but admitted "shape was useful, albeit not perfect, for differentiating cholesterol polyps from adenomas and cancer".[18] Their recommenda-

tion was for cholecystectomy for PLG less than 18 mm as they can be early-stage cancers but do not confirm the 10-mm cutoff. Sugiyama et al. attempted to differentiate benign and malignant PLG with the use of pre-operative US and EUS.[19] Fourteen percent of patients with PLG found to be between 6 and 10 mm on pre-operative US were indeed adenomas or adenocarcinomas. Aggregation of echogenic spots on EUS seemed to be pathognomonic for cholesterol polyps, and therefore, they recommended pre-operative EUS for all PLG greater than 5 mm. However, absence of these spots was unable to differentiate between benign and malignant. Additionally, statistical significance of this finding was not commented upon.

There have been three prospective trials that demonstrate a seemingly low malignant transformation rate.[20–22] In the first, Moriguchi et al. followed up 109 patients with gallbladder polyps of various sizes over 5 years. They concluded that most PLGs are benign despite pathological confirmation in only six patients, one of which developed gallbladder cancer during the study period. The second trial by Csendes et al. did not demonstrate new malignant changes during 71 months of follow-up. However, there were only 22 patients in the 6–10-mm cohort of which less than 25% had no pathological confirmation. Additionally, 4% of the patients who underwent cholecystectomy had neoplastic PLGs. Lastly, while Collet et al. also did not demonstrate malignant changes on US, they discouragingly lost 42% of patients to follow-up within 5 years. This demonstrates the trouble with compliance over long-term follow-up and opens the door for malignant transformation to slip by.

Our study identified three characteristics of the pre-operative ultrasound that were statistically significant risk factors for the presence of neoplasia. Vascularity and liver invasion were verified as common sense risk factors. Additionally, we found that not only was maximum diameter greater than or equal to 10 mm statistically significant but expanding the size criteria to 6 mm or larger also maintained significance. Importantly, 3.7% of PLGs≤10 mm were malignant in our series. A review of the literature confirms this finding within small polyps. Up to 13% of PLGs less than 10 mm in maximum diameter are neoplastic.[9,15,17,19,23,24] We also identified three potentially malignant adenomas (3.7%) that were between 6 and 10 mm. Due to these reasons, we recommend strong consideration for cholecystectomy for any polyp greater than 6 mm. Additionally, any polyp that demonstrates vascularity or invasion is symptomatic or is present in a patient with a history of PSC requires removal. If the patient and surgeon elect for observation rather than operation, then close follow-up with serial ultrasound should be performed. Any growth during this follow-up period is an indication for removal due to the potential for malignant transformation.

Given the low morbidity of cholecystectomy and the high mortality of gallbladder cancer, we feel that this approach is justified.[25] Additionally, it saves the labor-intensive and costly follow-up period. Recommending a follow-up schedule is problematic as it has been reported to be anywhere from 3 to 12 months.[7,26,27] The difficulty lays in that the rate of transformation from benign to dysplastic adenomas and eventually to malignancy is unknown and likely takes years.

US technology is improving, but over half of our study population had a discrepancy between the pre-operative US and the final pathology. Most of these were related to over diagnosing a PLG when one was not present. We hypothesize that the US probes were picking up small mucosal folds or misdiagnosing gallstones that did not have posterior shadowing or were immobile. As has been shown, PLG diameter is an important risk factor for the presence of a true polyp. However, 28% of PLG diameters were misrepresented by at least 4 mm. US can over- and underestimate maximum diameter, and therefore, size assessments can be misleading. US is therefore unable to reliably distinguish between non-neoplastic and neoplastic PLGs.

This is the first paper to systematically compare the pre-operative US characteristics of a PLG to its post-operative pathological analysis. Prior studies have involved pre-operative US but look exclusively at the maximum diameter of the PLG based on gross pathological exam. We believe that our method is a more valid assessment. Our goal is to define which patients require cholecystectomy pre-operatively in contrast to defining which patients should have undergone cholecystectomy once the specimen has been removed.

Our series further corroborates the adenoma to carcinoma sequence. The pathological analysis demonstrated benign adenomas, dysplastic adenomas with low- and high-grade dysplasia, and adenocarcinoma. All dysplastic lesions were associated with adenomatous changes. Additionally, one of the three adenocarcinomas was in the presence of high-grade dysplasia within a papillary adenoma.

Contrast-enhanced US has recently been reported for evaluation of the gallbladder. A contrast agent is injected intravenously, which allows for increased reflectivity of blood and enhanced spectral and color Doppler signals. There is enhanced visualization of the vascular supply to the PLG with an associated increased sensitivity in diagnosing gallbladder lesions. Unfortunately, the ability to differentiate benign from malignant polyps was limited.[14,28] Additionally, EUS can increase the imaging detail in order to help differentiate benign and malignant polyps. However, the sensitivity was low at 77.8%.[11] EUS also requires specialized endoscopy services, which are not available at all institutions.

This was a retrospective review with inherent associated difficulties. The contributing radiologist reviewed 79% of the US studies, but the remaining data were extracted from

the original radiology report, which did not necessarily contain all the analyzed information. Additionally, the PLG tended to be an incidental finding and therefore may have been imaged in a more cursory fashion. Lastly, there may be a selection bias in that all of the patients underwent surgical resection. However, these patients were identified in a similar fashion to how a primary care provider would discover PLGs, either as an incidental finding or as a potential cause for the patient's symptomatology. Despite these limitations, we believe that our conclusions are valid.

Conclusion

Gallbladder adenocarcinoma is a deadly disease, with early surgical resection as the only chance for cure. It is imperative to maintain vigilance in differentiating non-neoplastic from neoplastic PLGs so potentially lethal cases are identified early. There are known risk factors that increase the likelihood of malignancy in a PLG, but no definitive criteria have been identified. Maximum diameter is the most distinguishing characteristic and has been traditionally set at 10 mm based on the pre-operative ultrasound, but this was supported by post-operative histopathologic analysis. To date, all reported malignant PLGs have been 6 mm or greater, and up to 22% of PLGs≤ 10 mm are neoplastic based on pre-operative US in our study and gross pathological analysis in others. As we have shown, it is impossible to definitively differentiate non-neoplastic from neoplastic PLGs based on current imaging technology. In order to allow for the inherent discrepancies and to capture the vast majority of neoplastic PLGs, we recommend strong consideration for gallbladder resection to include PLGs with a maximum diameter of 6 mm or greater based on the pre-operative US in addition to all patients with PSC and any patient in whom diligent long-term follow-up cannot be completed. We also continue to offer cholecystectomy for lesions that demonstrate growth, vascularity, invasion, or symptoms.

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Surgical Resection Versus Palliative Chemoradiotherapy for the Management of Pancreatic Cancer with Local Venous Invasion: A Decision Analysis

Michael A. Abramson · Edward W. Swanson · Edward E. Whang

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Abstract
Background Benefit from pancreaticoduodenectomy (PD) combined with superior mesenteric-portal vein (SMV-PV) resection in the management of pancreatic adenocarcinoma with local venous invasion remains controversial.
Methods Using formal decision analysis, we compared survival associated with PD plus SMV-PV resection when applied to patients with pancreatic adenocarcinoma with isolated local venous invasion (Group 1) versus that achieved with palliative chemoradiotherapy when applied to patients with locally advanced pancreatic cancer (Group 2). Individual studies were identified using Medline. A total of 1,324 and 709 patients were analyzed for Groups 1 and 2, respectively. Patients with distant metastases were excluded.
Results Overall decision analysis favored surgical resection (Group 1) over palliative chemoradiotherapy (Group 2). Sensitivity analyses indicated that this decision is sensitive to the perioperative mortality rate and the percentage of surgical resections with microscopic (R1) or macroscopic (R2) residual tumor at the resection margin. In contrast, sensitivity analysis revealed that the decision is not sensitive to the percentage of cases in which true venous invasion by cancer is documented histologically.
Conclusions Surgical resection may confer a survival advantage over palliative chemoradiotherapy in select patients with pancreatic cancers with presumed local venous invasion.

Keywords Pancreatic adenocarcinoma · Pancreaticoduodenectomy · Survival · Decision analysis

Introduction

Pancreatic cancer is the fifth leading cause of cancer-related deaths in the USA, causing an estimated 33,370 deaths in 2007.[1] Surgical resection offers the only potential for cure for patients with this disease.

The benefit of surgical resection for the subset of patients with locally advanced pancreatic cancers with isolated portal vein and/or superior mesenteric vein (PV-SMV) invasion is controversial. Although it has been suggested that resection of these lesions can be performed safely (with acceptable long-term survival rates), the survival benefit of surgical resection over palliative chemoradiotherapy has not been confirmed in a randomized controlled trial.

As such, in this study, we conducted formal decision analysis in order to compare survival in patients with pancreatic cancer based on two competing treatment strategies; Group 1 patients underwent surgical resection (pancreaticoduodenectomy (PD) with venous resection and reconstruction) for pancreatic adenocarcinoma with isolated local venous invasion and Group 2 patients underwent palliative chemoradiotherapy for locally advanced pancreatic cancer.

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M. A. Abramson · E. W. Swanson · E. E. Whang (✉)
Department of Surgery, Brigham and Women's Hospital,
Harvard Medical School,
75 Francis Street,
Boston, MA 02115, USA
e-mail: ewhang1@partners.org

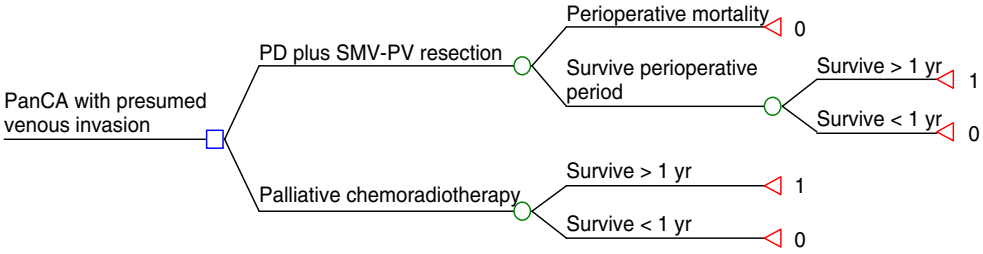

Figure 1 Decision tree comparing 1-year survival of all patients treated with PD plus PV-SMV resection versus those patients treated with palliative chemoradiotherapy.

Materials and Methods

Decision analysis is a quantitative method for estimating the effectiveness of alternative management strategies. Decision analysis was performed according to published guidelines.[2–6]

Data Sources

A systematic Medline search was conducted using the search term "pancreatic cancer AND vein resection" to identify English language publications containing data relevant to Group 1. Despite an extensive search of the literature, we were unable to identify studies reporting survival data specifically for patients with isolated local venous invasion treated solely with chemoradiation. As such, we used survival data for patients with locally advanced cancers treated with palliative chemoradiation as a proxy for survival among Group 2 patients. We believe this is an appropriate strategy, given that non-resected patients with Stage IIA (locally invasive; resectable; T3, N0, M0), Stage IIB (locally invasive; resectable; T1,2, or 3, N1, M0), and Stage III (locally advanced; unresectable; T4, any N, M0) disease are reported to have nearly identical 1-year survival rates (25.0%, 26.9% and 27.0%, respectively).[7,8] Upon detailed review of the selected articles for both groups, additional articles were subsequently identified that met inclusion criteria. Critical appraisal of each study was performed by the authors, and studies were selected on the basis of the inclusion criteria used for this analysis.

Inclusion and Exclusion Criteria

Letters, reviews without original data, animal studies, studies without survival data, and overlapping studies were all eliminated from the analysis. In studies that did not explicitly state survival time periods in the text, we have estimated survival using Kaplan–Meier Survival curves.

Perioperative mortality was defined as death within 30 days of the surgery. However, in-hospital or operative mortality was used as a substitute for perioperative mortality when death within 30 days of surgery was not reported.

Studies used for Group 1 included patients having pancreatic cancer with local invasion into the portal vein and/or superior mesenteric veins. All studies meeting these criteria were included regardless of the extent of lymph node dissection and/or venous resection. In some of the studies, survival data included patients undergoing simultaneous vein and arterial resections. Additionally, some studies included in our analysis included patients undergoing additional neoadjuvent and/or adjuvant therapies. Studies used for Group 2 included patients with locally advanced pancreatic cancers who received palliative chemoradiotherapy. Studies were included regardless of the

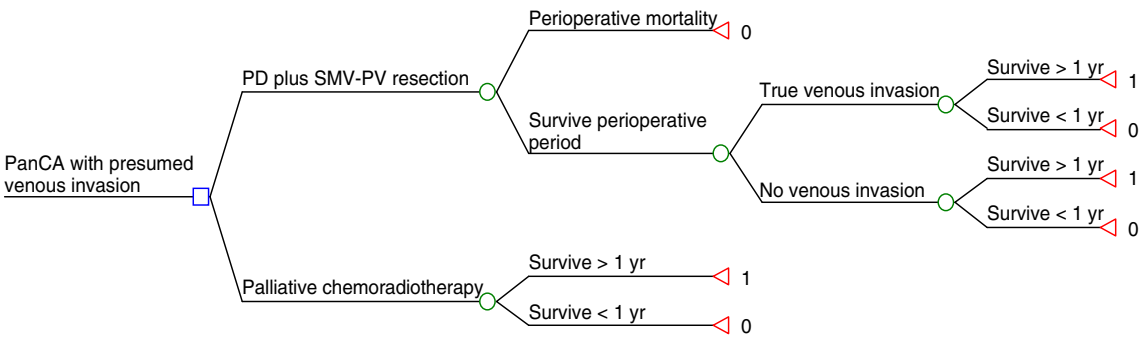

Figure 2 Decision tree comparing 1-year survival of the subset of patients treated with PD plus PV-SMV resection accounting for documented histopathologic invasion status of cancer into the portal and/or superior mesenteric vein and versus those patients treated with palliative chemoradiotherapy.

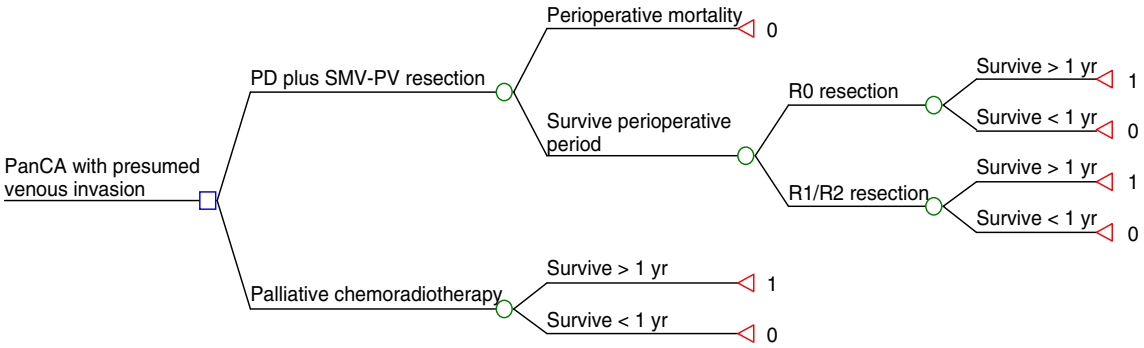

Figure 3 Decision tree comparing 1-year survival of the subset of patients treated with PD plus PV-SMV resection accounting for documented R-status at the surgical resection margin versus those patients treated with palliative chemoradiotherapy.

type or duration of the treatment regimen. Some studies in this group included patients with incompletely resected pancreatic cancer with residual disease. Patients were excluded from both Groups 1 and 2 if there was any evidence of metastatic disease.

Decision Analysis Models and Calculations

Decision tree design and analysis was performed using TreeAge Pro 2007 software (TreeAge Software, Williamstown, MA, USA). Decision trees used in this analysis are

Table 1 Published Studies Included in the Surgical Resection Group (Group 1)

Year published	Inclusion period	Authors	Institution	Patients
2008	1994–2005	Yekebas et al.[10]	University Medical Centre Hamburg-Eppendorf (Germany)	100
2007	1998–2005	Al-Haddad et al.[11]	Mayo Clinic (Jacksonville)	22
2006	1996–2004	Shimada et al.[12]	National Cancer Center (Tokyo, Japan)	86
2006	1989–2003	Carrere et al.[13]	Hopital Beaujon, University Paris VII (France)	45
2006	1981–2005	Nakao et al.[14]	Nagoya University (Japan)	186
2006	1994–2004	Riediger et al.[15]	University Hospitals of Rostock and Freiburg (Germany)	26
2005	1999–2003	Zhou et al.[16]	Shanghai Institute of Digestive Surgery (China)	32
2005		Koniaris et al.[17]	University of Miami School of Medicine	11
2004	1998–2002	Poon et al.[18]	Queen Mary Hospital, University of Hong Kong (China)	12
2004	1990–2002	Tseng et al.[19]	University of Texas, M.D. Anderson Cancer Center	110
2004	1994–2003	Bin Li et al.[20]	Multiple hospitals in China	79
2003		Howard et al.[21]	Indiana University School of Medicine	13
2003	1992–2001	Nakagohri et al.[22]	National Cancer Center East (Japan)	33
2003	1983–2000	Aramaki et al.[23]	Oita Medical University (Japan)	22
2002	1990–1997	Kawada et al.[24]	Hokkaido University (Japan)	28
2002	1987–2000	Sasson et al.[25]	Fox Chase Cancer Center and Temple University	25
2002	1980–2001	Hartel et al.[26]	University-Hospital Mannheim (Germany)	68
2001	1983–1998	Shibata et al.[27]	Sendai City Medical Center and Iwate Medical University (Japan)	28
2001	1992–1998	van Geenen et al.[28]	Academic Medical Center (Netherlands)	34
2001	1990–1999	Bachellier et al.[29]	Hopital Universitaire de Hautepierre (France)	21
2001	1996–1999	Park et al.[30]	Samsung Medical Center (Korea)	25
2001	1965–1998	Kinoshita et al.[31]	Kurume University School of Medicine (Japan)	37
1999	1973–1992	Launois et al.[32]	Centre Medico Chirurgical Saint Vincent (France)	14
1998	1981–1996	Civello et al.[33]	Catholic University School of Medicine (Rome, Italy)	7
1998	1976–1997	Naganuma et al.[34]	Mie University School of Medicine (Japan)	30
1996	1983–1995	Harrison et al..[35]	Memorial Sloan-Kettering Cancer Center	58
1996		Roder et al.[36]	Technische Universitat Munchen (Germany)	31
1996	1971–1993	Klempnauer et al.[37]	Hannover Medical School (Germany)	18
1995	1970–1994	Yeo et al.[38]	Johns Hopkins Medical Institutions	10
1994	1983–1992	Allema et al.[39]	Academic Medical Centre (Netherlands)	20
1994	1976–1992	Takahashi et al.[40]	Keio University School of Medicine (Japan)	63
1992	1984–1989	Ishikawa et al.[41]	The Center for Adult Diseases (Osaka, Japan)	30

shown in Figs. 1, 2, and 3. Figure 1 shows the decision tree comparing 1-year survival of all patients treated with PD plus PV-SMV resection versus those patients treated with palliative chemoradiotherapy. Figure 2 shows the decision tree comparing 1-year survival of the subset of patients treated with PD plus PV-SMV resection accounting for documented histopathologic invasion status of tumor into the portal and/or superior mesenteric vein versus those patients treated with palliative chemoradiotherapy. Figure 3 shows the decision tree comparing 1-year survival of the subset of patients treated with PD plus PV-SMV resection accounting for documented R-status at the surgical resection margin versus those patients treated with palliative chemoradiotherapy.

Weighted means were calculated for each variable and used as baseline estimates, taking into account the number of patients contributing to each outcome. As the outcome of interest in this analysis was survival at a given time point, a utility (payoff) of 1 was assigned for a patient surviving to that time point, and a utility of 0 was assigned for a patient surviving less than to that time point.

Sensitivity Analysis

One-way sensitivity analysis was performed for variables in the decision models to determine the impact of uncertainty in the estimates of probabilities. Threshold values were calculated for variables that would lead to a change in the preferred strategy when traversed. If the decision outcome to select one treatment strategy over the other did not change over the range of the variable being manipulated, the decision was considered to be not sensitive to this variable and, thus, no threshold was identified for that variable. Alternatively, if the decision outcome to select one treatment strategy over the other did change over the range of the variable being manipulated, the decision was considered to be sensitive to this variable, and the value at which the optimal strategy changed was considered to be the "threshold value."

Results

Analysis of Data Used

Studies used in the analysis are shown in Tables 1 and 2 for Groups 1 and 2, respectively. Overall, a total of 32 studies including 1,324 patients and 19 studies including 709 patients were used to calculate baseline probabilities for Groups 1 and 2, respectively.

Variables used in the decision trees, calculated weighted means, and ranges found in the literature are shown in Table 3. Overall decision analysis favored surgical resection over palliative chemoradiotherapy with 1-year survival probabilities of 55% and 39% for Groups 1 and 2, respectively. Similarly, analysis favored surgical resection over palliative chemotherapy when 3- and 5-year survivals were used as the outcome of interest (data not shown).

Sensitivity Analysis

One-way sensitivity analyses varying the: (1) perioperative mortality rate, (2) the percentage of cases in which true

Table 2 Published Studies Included in the Chemoradiotherapy Group (Group 2)

Year published	Inclusion period	Authors	Institution	Patients	Treatment Regimen
2007	2004–2005	Ikeda et al.[42]	Nat Cancer Center Hosp. East, Japan	21	Radiation+S-1
2007	2001–2003	Haddock et al.[43]	Mayo Clinic	48	Radiation+Gemciabine+Cisplatin
2005	1983–1989	Cohen et al.[44]	Fox Chase Cancer Center	55	Raditation+5-FU+MMC
2005	2000–2003	Mishra et al.[45]	Wake Forest	20	Radiation+Gemcitabine+Irinotecan
2004	1998–2000	Rich et al.[46]	University of Virgina	109	Radiation+Paclitaxel
2003	1999	Blackstock et al.[47]	Wake Forest	43	Radiation+Gemcitabine
2003	1998–2001	Martenson et al.[48]	Mayo Clinic	26	Radiation+Gemciabine+Cisplatin
2002	1997–1999	Epelbaum[49]	Technicon-Israel Institute of Tech	20	Radiation+Gemcitabine
2001	1996–1998	Wolff et al.[50]	MD Anderson	18	Radiation+Gemcitabine
2001		Safran et al.[51]	Brown University	44	Radiation+Paclitaxel
2000		Talamonti et al.[52]	Northwestern University	7	Radiation+5-FU+Gemcitabine
1997	1993–1996	Ishii et al.[53]	Nat. Cancer Center Hosp., Tokyo	20	Radiation+5-FU
1995		Whittington et al.[54]	University of Pennsylvania	16	Radiation+5-FU
1981		Moertel et al.[55]	Mayo Clinic	86	6000 rads+5-FU
1969		Moertel et al.[56]	Mayo Clinic	32	Radiation+5-FU
2005	2001–2003	Louvet et al.[57]	Hospital St. Antoine	51	Gemcitabine+Oxaliplatin
2004		Rocha Lima et al.[58]	University of Miami	24	Gemcitabine
2002	1997–1998	Bramhall et al.[59]	Queen Elizabeth Hospital	32	Gemcitabine
2001	1997–2000	McGinn et al.[60]	University of Michigan	37	Radiation+Gemcitabine

Table 3 Study Variables

Variable	Studies analyzed	Patients	Weighted mean (%)	Range (%) in the literature
1-year survival for treatment with chemoradiation	13	567	39	17–51
1-year survival for treatment with surgical resection	26	1151	57	22–94
Perioperative mortality	28	1303	3	0–15
Histopathologic proven vein invasion	23	852	61	3–100
1-year survival for treatment with surgical resection given true histopathologic vein invasion	10	219	53	14–80
1-year survival for treatment with surgical resection given no histopathologic vein invasion	9	109	62	0–81
R1 or R2 resections	22	921	34	8–85
1-year survival for treatment with surgical resection given an R0 resection	3	63	62	45–75
1-year survival for treatment with surgical resection given an R1 or R2 resection	3	50	34	17–61

venous invasion by cancer is documented histologically, and (3) the percentage of surgical resections with microscopic (R1) or macroscopic (R2) residual tumor at the resection margin are shown in Figs. 4, 5, and 6, respectively.

The decision to perform surgical resection versus chemoradiation is sensitive to manipulation of the perioperative mortality rate. At the baseline perioperative mortality of 3.3%, decision analysis favors resection over chemoradiation. However, at a perioperative mortality rate higher than 31%, (intersection of lines in Fig. 4), decision analysis favors treatment with chemoradiation over surgical resection.

One-way sensitivity analysis revealed that an increase in the percentage of cases in which true venous invasion by cancer is documented histologically resulted in a decrease in the 1-year survival of those patients undergoing surgical resection (Fig. 5). However, the decision analysis favored surgical resection over chemoradiation regardless of the percentage of tumors with histopathologically proven invasion, and thus, the decision is not sensitive to this variable.

Finally, one-way sensitivity analysis demonstrated the decision to treat with surgical resection over chemoradiation is sensitive to the percentage of surgical resections with either microscopic (R1) or macroscopic (R2) residual tumor at the resection margin. At a probability of R1 plus R2 resections greater than 77%, surgical resection is no longer the favored strategy (Fig. 6).

Discussion

As far as we are aware, this is the first study to utilize decision analysis to assess the potential survival benefit of surgical resection for patients with pancreatic cancer with local venous invasion. Given a lack of randomized controlled trials, decision analysis provides a useful alternative method for comparing these two treatments.

In their recent article, Siriwardana et. al. performed a systematic review of the literature of outcomes associated

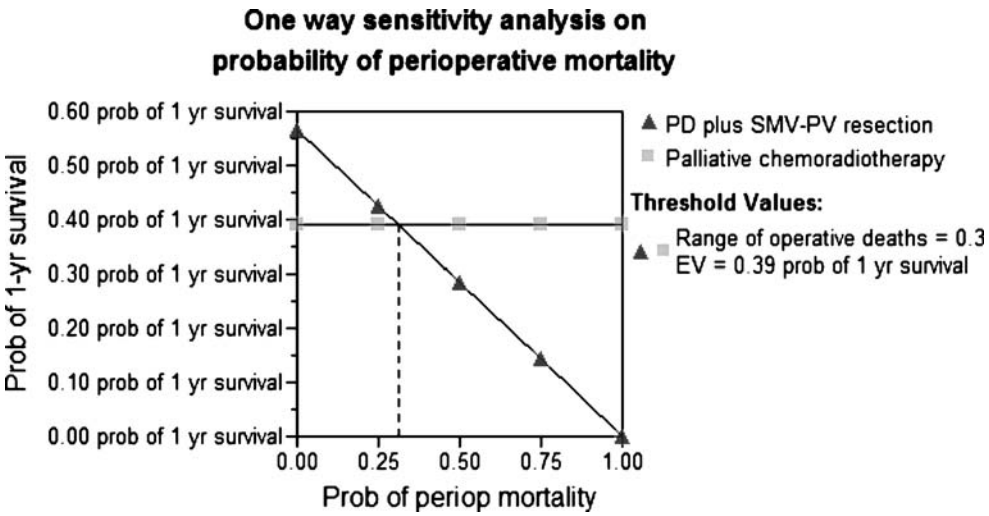

Figure 4 One-way decision analysis varying the perioperative mortality rate over a range of values. The decision to perform surgical resection versus chemoradiation was sensitive to manipulation of this variable. Decision analysis favored treatment with chemoradiation over surgical resection at a perioperative mortality rate higher than 30% (*intersection of two lines*).

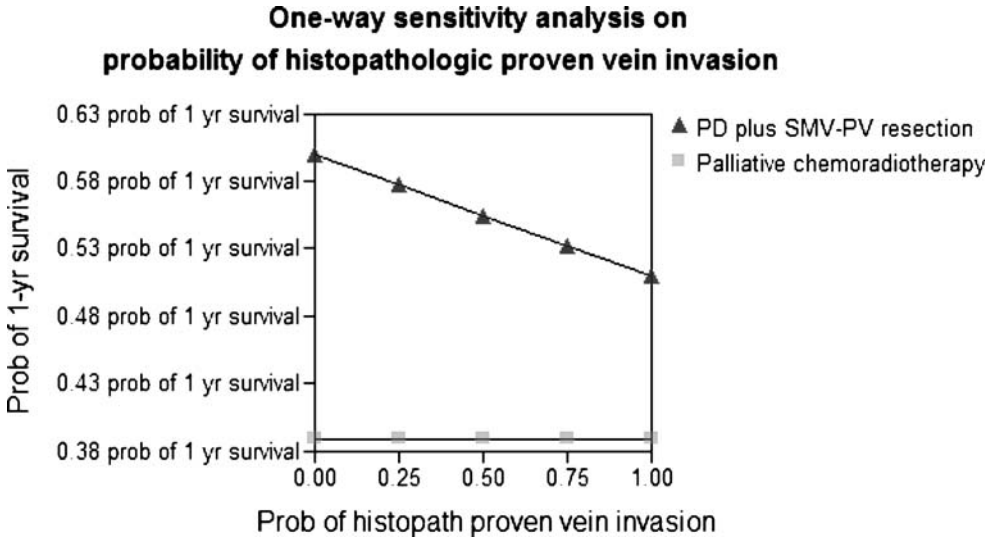

Figure 5 One-way decision analysis varying the percentage of tumors with histopathologic proven invasion into the portal and/or superior mesenteric veins. As this variable increased, the 1-year survival of those patients undergoing surgical resection decreased (note the negative slope of the *line marked with triangles*). However, the decision analysis favored surgical resection over chemoradiation regardless of the percentage of tumors with histopathologic proven invasion (i.e., no threshold was reached).

with synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer.[9] The authors pooled data on categories relating to the operation, complications, histopathology, and overall outcome and concluded that even with radical resection, cures are unlikely for patients with tumors involving the portal vein.[8]

A decision analysis study, such as ours, is not without potential limitations, which we enumerate here. As we have pooled many studies in order to determine baseline probabilities, there is considerable variability within both groups compared in this study, along with some overlap of the two groups in this study. In the surgical group, studies differed in the types of adjuvant and/or neoadjuvant therapies, criteria used for resectability, preoperative imaging studies, curative-resection rates, surgical techniques (e.g., venous reconstructive procedures), extent of resection (e.g., removal of lymph nodes), and tumor location, for example. Similarly, the patient selection and treatment regimens varied widely in the palliative chemoradiotherapy group. To account for this variability in published study data, we completed sensitivity analyses over a wide range of values for the probability of perioperative mortality, probability of histopathologic vein invasion and the probability of an R1 or R2 resection to determine threshold values that would lead to a change in the preferred strategy when traversed.

Decision analysis studies can be limited by paucity of data for specific patient subgroups. Although there are several published reports containing survival data for surgically treated patients based on histopathologically documented invasion status of cancer into the portal and/or superior mesenteric vein, there are fewer reports

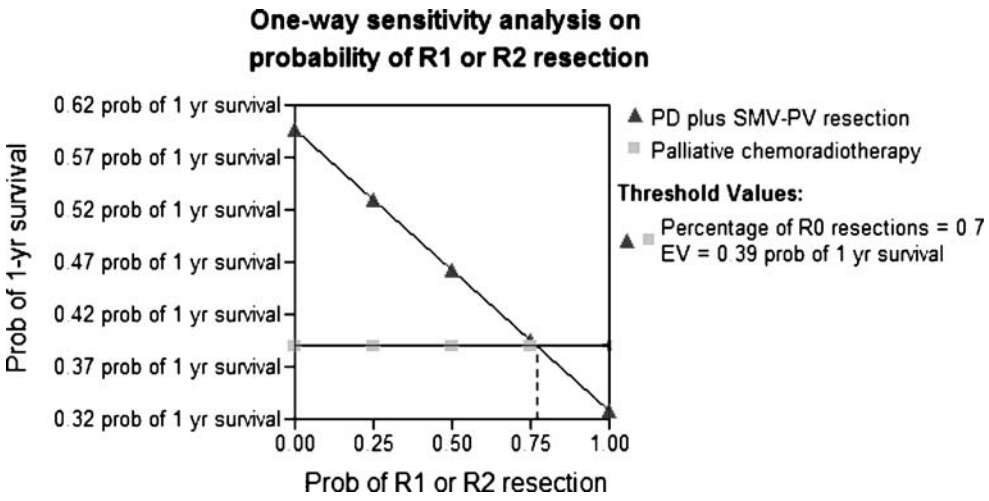

Figure 6 One-way sensitivity analysis varying the percentage of surgical resections with either microscopic (R1) or macroscopic (R2) residual tumor at the resection margin. At a probability of R1 plus R2 resection greater than 80%, surgical resection was no longer the favored treatment strategy.

containing survival data for surgically treated patients (those treated with portal and/or superior mesenteric vein resection) based on documented R-status at the surgical resection margin (Table 3). Furthermore, as far as we are aware, there are no published reports that contain survival data based on both of these variables in the same patient cohort. To overcome this limitation, we elected to analyze survival data using three separate decision trees instead of a single tree. This strategy allowed us to include many more studies than would have been possible for a single decision tree approach.

Finally, as we have noted earlier in our methods and discussion, our study compared two groups of patients that may not be identical with respect to stage distribution, comorbidity profiles, and other variables. For example, although most patients categorized into Group 1 of our study had cancer invasion limited to the portal vein and/or superior mesenteric vein (stage IIA or IIB disease), some of these patients had invasion into the superior mesenteric artery (stage III disease) for which arterial resection was performed.[7] For Group 2, the reported data do not permit determination of the distribution of patients among stages IIA, IIB, and III; therefore, it is possible that a greater percentage of Group 2 than Group 1 patients had stage III disease. Nonetheless, patients with nonresected stages IIA, IIB, and III pancreatic adenocarcinoma have virtually indistinguishable 1-year survival rates (25.0%, 26.9%, and 27.0%, for stages IIA, IIB, and III, respectively).[8] Given that the primary endpoint of our study was 1-year survival and all patients included in our study had stage IIA, IIB or III disease, we believe that Groups 1 and 2 are comparable for the purposes of this analysis.

Conclusion

In conclusion, we have determined that surgical resection may confer a survival advantage over palliative chemo-radiotherapy in select patients with pancreatic cancers with presumed invasion into local veins. We recommend that authors report survival statistics based on histopathologic proven vein invasion and R-status so that a more through evaluation of this data may be completed in the future.

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Practical Limitations of Bioresorbable Membranes in the Prevention of Intra-Abdominal Adhesions

Rizal Lim · Jonathan M. Morrill · Ryan C. Lynch · Karen L. Reed · Adam C. Gower · Susan E. Leeman · Arthur F. Stucchi · James M. Becker

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Abstract
Introduction Intra-abdominal adhesions are a significant source of postoperative morbidity. Bioresorbable barriers composed of hyaluronic acid and carboxymethylcellulose (HA/CMC) reduce adhesion formation by physically separating injured or healing peritoneal surfaces. To assess whether the efficacy of a physical barrier can extend beyond the site of application, we evaluated the effectiveness of an HA/CMC barrier in preventing adhesions distal to the site of placement.
Methods Adhesions were induced in rats by creating peritoneal ischemic buttons on either side of a midline incision. An HA/CMC barrier (Seprafilm™ Genzyme) was intraoperatively placed either under the midline incision, unilaterally over half the ischemic buttons, or bilaterally over all ischemic buttons. Control buttons received no HA/CMC. On day 7 adhesions were scored. In similar experiments, peritoneal fluid was collected at 24 h to assess the effects of HA/CMC on tissue plasminogen activator activity.
Results Placement of HA/CMC under the midline incision did not reduce adhesion formation to distal ischemic buttons (72±7%) compared to controls (80±8%). Unilateral placement of HA/CMC significantly ($p<0.05$) reduced adhesion formation to those ischemic buttons over which the barrier was applied (35±7%) compared to both contralateral (83±9%) and control (80±8%) ischemic buttons. The bilateral application of HA/CMC also significantly ($p<0.05$) reduced adhesion formation to all ischemic buttons compared to controls (22±7% vs. 66±7%, respectively). HA/CMC did not affect peritoneal tPA activity.
Conclusions Effective adhesion reduction by the physical barrier HA/CMC appears to be limited to the site of application in this rat model. Despite the presence of a bioresorbable membrane at predicted sites of adhesion formation in the peritoneal cavity, adhesions readily form to distal unprotected sites.

Keywords Intraabdominal adhesions · Peritoneum · Hyaluronic acid/carboxymethylcellulose · Bioresorbable barriers · Seprafilm · Tissue plasminogen activator · Peritoneal fibrinolytic activity

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R. Lim · J. M. Morrill · R. C. Lynch · K. L. Reed · A. C. Gower · S. E. Leeman · A. F. Stucchi · J. M. Becker (✉)
Department of Surgery, Boston University School of Medicine,
88 East Newton Street,
Boston, MA 02118, USA
e-mail: James.Becker@BMC.org

Introduction

Although the existence of adhesions was documented more than 250 years ago, it was not until the advent of abdominal surgical procedures near the beginning of the twentieth century that the long-term consequences of intra-abdominal adhesions were recognized.[1] Since then many clinical and basic science studies have been conducted aimed at achieving a better understanding of postoperative adhesion formation. Although these studies have certainly increased our basic knowledge of adhesion formation and have led to improved surgical techniques and methods to reduce adhesions, adhesions still remain a significant, unresolved postoperative complication.

Postoperative adhesions are now the most frequent complication of abdominal surgery, especially operations

to the pelvic area and the lower gastrointestinal tract.[2] It is estimated that the incidence of adhesion formation is as high as 94–100% in patients following certain open colorectal operations.[3,4] Postoperative peritoneal adhesions are associated with serious and even life-threatening postoperative complications such as adhesive small-bowel obstruction, infertility, chronic pelvic pain, difficult reoperative surgery and bowel ischemia.[5] Five percent of patients will develop adhesive small bowel obstructions after abdominal surgery requiring surgery and approximately 30% of those patients will experience recurring symptoms [6] up to 30 years or more.[7]

Adhesion-related complications, whether surgery is required or not, are now recognized as a significant burden to the health care system. Adhesion-related readmissions can be very costly and can result in significant morbidity and mortality.[8,9] In the USA, adhesive small bowel obstructions led to over 2,200 deaths in 2001 and greater than 67,000 hospital admissions with the length of hospital stay averaging 9.8 days. The financial burden to the US healthcare system of these adhesion-related hospital admissions is estimated to be greater than $5 billion dollars annually.[10] A study from the UK suggests that using a low-cost anti-adhesion product that reduces adhesions by 25% for 1 year could save over 40 million Euros (~$62 million dollars) in a 10-year period.[11] Despite the fact that adhesions have been recognized for centuries and research on adhesion pathophysiology and prevention was documented in the medical literature in the early 1900s, adhesions remain a significant postoperative complication suggesting that current methods of preventing adhesions require substantial improvement.[12]

The only approved adhesion prevention methods in the USA are the physical barriers such as Seprafilm Adhesion Barrier™ (Genzyme Biosurgery, Cambridge, MA, USA) and Adept Adhesion Reduction Solution® (Baxter Healthcare Corporation, Deerfield, IL, USA). The most commonly used and recognized of these products is Seprafilm™, a bioresorbable membrane composed of hyaluronic acid and carboxymethylcellulose (HA/CMC) typically placed intraperitoneally under the midline incision at the end of an operation. Bioresorbable HA/CMC barriers reduce adhesion formation by preventing the close apposition and adherence of injured or healing peritoneal tissues.[13] Studies have shown that HA/CMC is highly effective at reducing postoperative peritoneal adhesions where it is placed, mainly to the midline incision;[14,15] however, other studies showed limited effectiveness at preventing adhesive small bowel obstruction in patients undergoing gastrectomy for gastric cancer.[16] Thus, the efficacy of HA/CMC may be limited strictly to adhesions forming to the midline incision under which it is placed and alone, whether HA/CMC barriers effectively prevent the long-term consequences of adhesions such as adhesive small bowel obstruction may require further investigation.[17]

Studies in humans and animal models have shown that peritoneal trauma initiates an inflammatory response that leads to the deposition of a fibrin-rich exudate on injured peritoneal surfaces.[18] If the fibrinous exudate is not resolved within 2–3 days after surgery, permanent fibrous adhesions will likely form.[19] Peritoneal restitution is mediated, in part, by a very active peritoneal fibrinolytic system that rapidly degrades the fibrinous exudate.[20] However, the inflammatory response to peritoneal trauma can overwhelm normal peritoneal fibrinolytic mechanisms.[21–23] The fibrin matrix is degraded by plasmin, a protease converted from inactive plasminogen by tissue-type plasminogen activator (tPA), the primary plasminogen activator in the peritoneum.[20] Surgical trauma impairs peritoneal fibrinolytic activity by reducing tPA activity.[24] Although physical barriers prevent the newly formed fibrin matrix from adhering to an opposing surface and thus preventing adhesion formation, the changes in peritoneal fibrinolytic activity after the application of an HA/CMC barrier has not been fully elucidated.

Since adhesion formation can occur throughout the peritoneal cavity, the ideal adhesion prevention method should focus on more widespread adhesion prevention without compromising peritoneal fibrinolytic activity. To date, there have been no investigations of the effectiveness of HA/CMC in preventing adhesion formation at areas away from the site of application. Therefore, utilizing our well-defined, objective rat model of adhesion formation, the objectives of this study were twofold: first, to evaluate the efficacy of HA/CMC in preventing postoperative adhesions away from the site of placement and second, to determine whether the presence of HA/CMC affects peritoneal fibrinolytic activity.

Material and Methods

Material Seprafilm Adhesion Barrier™ (HA/CMC) was obtained from Genzyme Biosurgery (Cambridge, MA, USA).

Animals Forty-seven male Wistar rats, weighing 200–250 g were obtained from Charles River Laboratories (Wilmington, MA, USA). Animals were housed in rooms at a constant 25°C with 12-h light–dark cycles. Food (Purina, No. 5001) and water were provided ad libitum. All procedures and animal care were approved by the Institutional Animal Care and Use Committee at Boston University School of Medicine and performed in accordance with recommendations outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Induction of Intra-Abdominal Adhesions and Experimental Design General anesthesia was induced in rats and main-

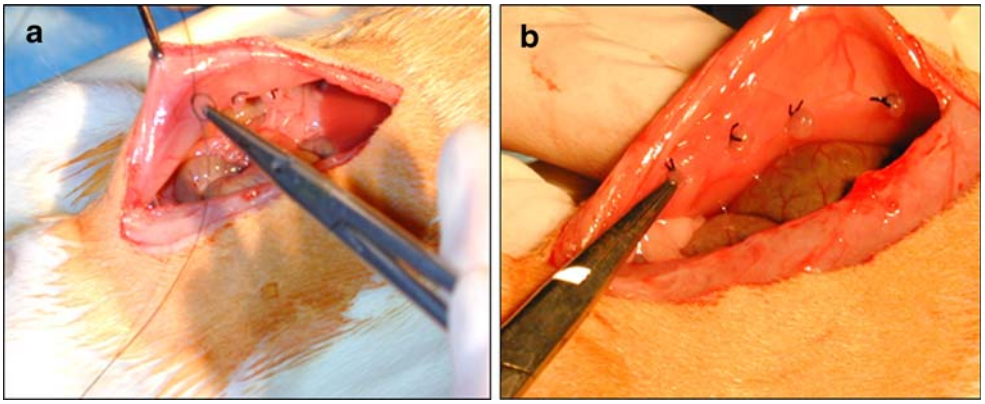

Figure 1 **a** To create ischemic buttons, 5 mm of peritoneal tissue was grasped with a hemostat and ligated at the base of the segment with a 4–0 silk suture. **b** Depending on the size of the animal, three or four ischemic buttons are placed on the peritoneal sidewall of male Wistar rats. Reproduced with permission from Reed et al.[25]

tained with continuous isoflurane 2–4% in 100% oxygen. The abdomen was shaved using clippers, prepared with 7.5% providone-iodine solution and a midline laparotomy was performed. Ischemic buttons were created as previously described.[25] Briefly, a 5 mm piece of peritoneum was grasped with a hemostat and ligated at the base with a 4–0 silk suture. Three to four ischemic buttons on each side of the peritoneum were placed 1 cm from the midline incision and 1 cm apart (Fig. 1). In the first experiment HA/CMC barrier was placed intraoperatively either under the midline incision (Fig. 2b) or unilaterally over the ischemic buttons on the left side of the peritoneum (Fig. 2c) (n=6 midline, n=17 unilateral, and n=6 control). In a second set of experiments, the HA/CMC barrier was placed bilaterally over all ischemic buttons (Fig. 2d) (n=9 bilateral and n=9 control). The abdomen and skin were closed using braided absorbable suture and clips, respectively. Postoperative pain was addressed with subcutaneous injections of buprenorphine (0.1 mg/kg body wt) at the time of operation and as needed every 12 h postoperation for up to six doses. On postoperative day 7, following CO_2 euthanasia, adhesion formation was quantified in a blinded fashion with each animal receiving a percent adhesion score based on the number of ischemic buttons with attached adhesions.

Peritoneal tPA Activity Assay To evaluate total peritoneal fibrinolytic activity, tPA activity was measured in peritoneal fluid samples 24 h after surgery using a colorimetric, enzymatic assay as previously described.[26] Briefly, peritoneal fluid samples containing acetated buffer were acidified with 0.2 volumes 0.375 N HCl and then diluted tenfold with distilled water. Diluted samples were then assayed in duplicate in a 96-well plate containing 50 uL of tPA stimulator (0.6 mg/ml cyanogen bromide digested fibrinogen, American Diagnostica, Stamford, CT, USA). Then, 150 ul of assay buffer is added to each well (16.7 μg/ml human plasminogen (Athens Research and Technologies, Athens, GA, USA), 667 μM S-2251 substrate (American Diagnostica), and 20 mM Tris, pH 8.3). Change in absorbance was measured with a Spectra Max 250 spectrophotometer (Molecular Devices, Sunnyvale, CA, USA) at 405 and 490 nm (calibration blank) at 37°C over 6 h. The activity of tPA was determined by extrapolation by a tPA standard curve (human Calbiochem, San Diego, CA, USA).

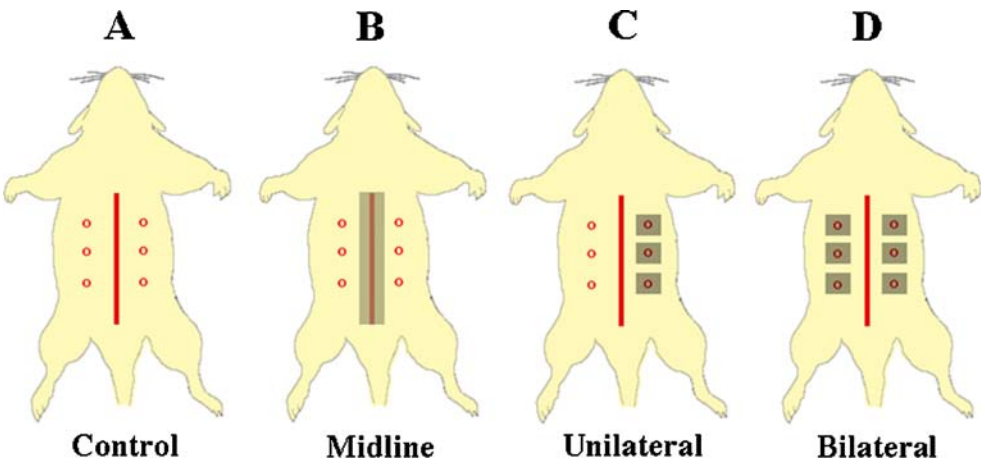

Figure 2 Schematic illustrating the placement of ischemic buttons (*open circles*) and the hyaluronic acid/carboxymethylcellulose (HA/CMC) barrier (*gray shaded areas*) within the rat abdomen, relative to the midline incision (*line*). From left to right: **a** operative control (no HA/CMC), **b** midline application of HA/CMC, **c** unilateral application of HA/CMC, and **d** bilateral application of HA/CMC barrier.

Statistical Analysis Data were analyzed with the Sigma Stat program (SPSS, Chicago, IL, USA) with one-way analysis of variance (ANOVA). When significant effects were detected ($p<0.05$), the difference between specific means was determined by the Holman–Sidak test. If a test of normality failed, Dunn's test of ANOVA by ranks was used. Differences were considered to be statistically significant if $p<0.05$.

Results

Efficacy of the HA/CMC Barrier in Reducing Adhesion Formation is Limited to the Site of Placement HA/CMC applied at the midline incision did not significantly decrease adhesion formation to ischemic buttons (72±7%) on either side of the peritoneum compared with control animals which had 80±8% adhesion formation (Fig. 3a). When the HA/CMC was applied unilaterally over ischemic buttons on the left side, significant adhesion reduction ($p<0.05$) was limited to areas of barrier placement (35±7%) compared to both the controls (80±8%) and the contralateral ischemic buttons (83±9%; Fig. 3b). There was no significant difference in adhesion formation between the controls and the contralateral untreated ischemic buttons. When HA/CMC was applied bilaterally to all ischemic buttons there was a 66% reduction ($p<0.05$) in adhesion formation compared to controls (Fig. 4 66±7% vs 22±6.7%, respectively).

There was no evidence of abscess formation or impaired wound healing in any animals that received HA/CMC. HA/CMC placed under the midline or over ischemic buttons remained in place at 24 h but was in a gel form. HA/CMC was fully biodegraded at 7 days.

HA/CMC does not Affect Peritoneal tPA Activity The bilateral administration of HA/CMC for 24 h, which represented the greatest amount of HA/CMC applied, had no affect on peritoneal fluid tPA activity at 24 h after surgery compared with operated controls (Fig. 5; 3.21±0.91 vs 2.1±0.41 U/ml, respectively).

Discussion

To our knowledge, a systematic study examining the effects of an HA/CMC barrier on adhesion formation at sites distal to placement has not been conducted. The results from this study show that in a well-defined, objective rat model of adhesion formation, the effectiveness of an HA/CMC barrier in preventing adhesion formation is limited exclusively to the site of placement. The HA/CMC barrier did not reduce adhesions at sites distal to the area of

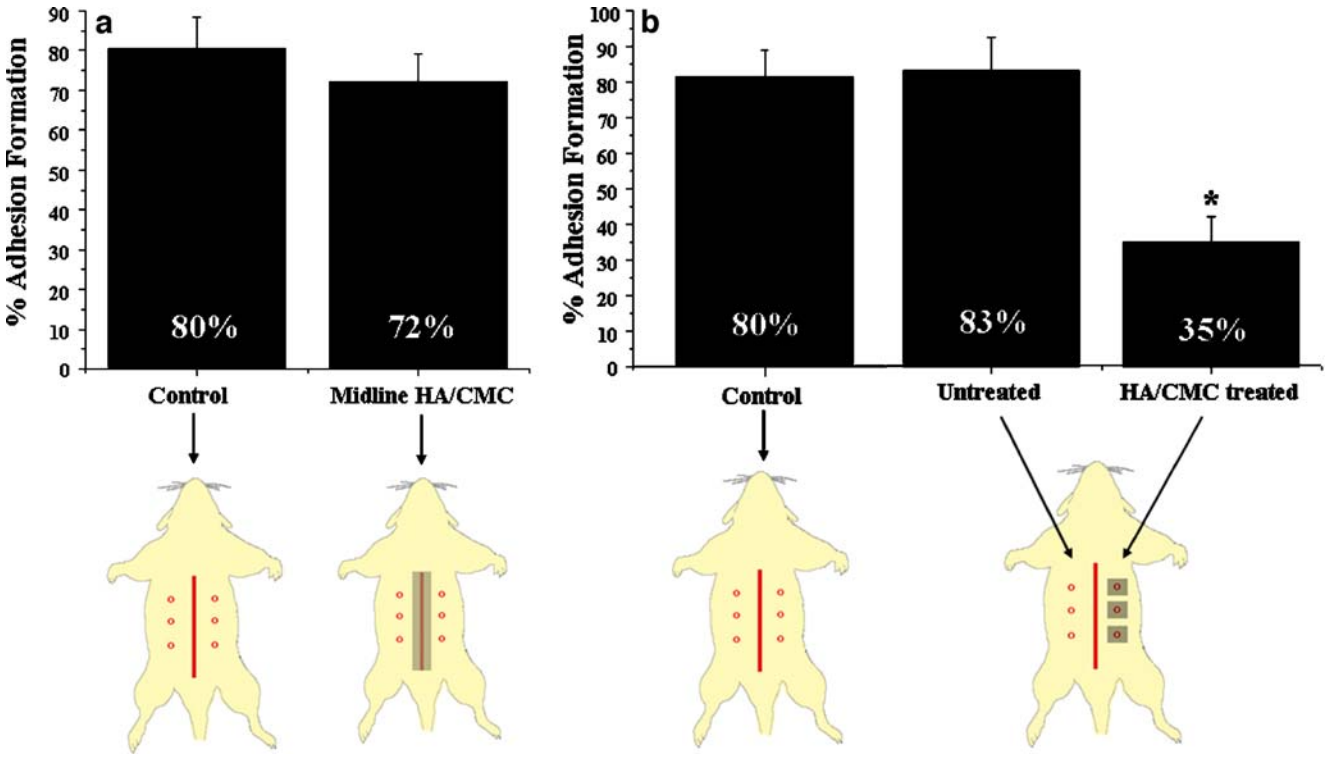

Figure 3 **a** The percent adhesion formation to ischemic buttons in animals with the application of hyaluronic acid/carboxymethylcellulose (HA/CMC) barrier under the midline incision or **b** unilaterally over half of the ischemic buttons. Data are expressed as the mean± SEM. *$p<0.05$ compared to both untreated buttons in same animals and to control animals.

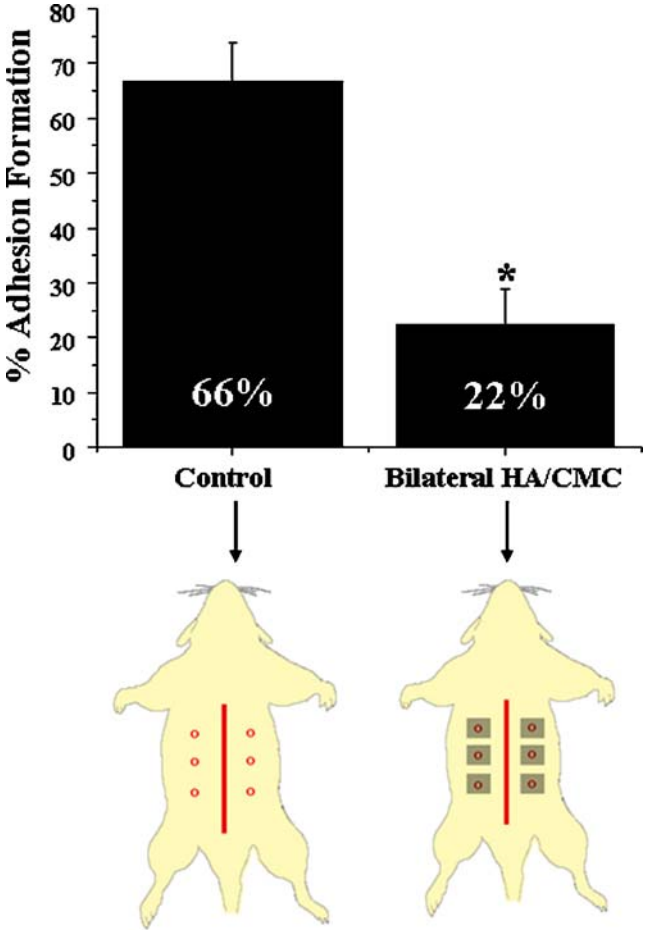

Figure 4 The percent adhesion formation to ischemic buttons in animals with bilateral application of the hyaluronic acid/carboxymethylcellulose (HA/CMC) barrier. Data are expressed as the mean±SEM. *$p<0.05$ compared to control animals.

application. When HA/CMC was placed at the midline in the classic fashion, adhesions still formed laterally at the ischemic button sites. When HA/CMC was placed over half of the ischemic buttons (unilateral placement), it significantly reduced adhesion formation only to those buttons but had no affect on adhesion formation to the untreated or unprotected ischemic buttons on the contralateral side. As would be expected, covering all ischemic buttons with the HA/CMC barrier (bilateral placement) resulted in significantly reduced adhesion formation to every button. However, the bilateral placement of HA/CMC did not affect peritoneal fibrinolytic activity. These results demonstrate that, in a rat model, HA/CMC effectively reduces adhesions when placed between the viscera and known abdominal wall defects; however, HA/CMC may not prevent adhesions at other ischemic areas within the peritoneum which could include between adjacent loops of bowel where adhesions are strongly associated with adhesion related small-bowel obstruction.[27] These data indicate that although the HA/CMC barriers are highly effective were placed, their efficacy may be substantially improved by the coadministration of a more immediately soluble anti-adhesion adjuvant to reduce adhesion formation throughout the peritoneal cavity.

The advent of physical barriers such as HA/CMC bioresorbable membranes significantly reduced the incidence of adhesion formation to the midline incision.[14] However, as noted earlier, the efficacy of physical barriers in reducing the long-term adhesion-related complications, especially adhesive small bowel obstruction, may still require further investigation.[17] Despite the recent study showing that adhesive small bowel obstruction requiring reoperation was significantly reduced by Seprafilm,[28] other studies have demonstrated that Seprafilm did not significantly reduce the incidence of small bowel obstruction in patients undergoing gastrectomy for gastric cancer.[16]

At the present time in the USA, the HA/CMC barrier Seprafilm™ is only available in the form of a sheet that is placed between the abdominal wall and underlying viscera thereby physically preventing adherence and subsequent adhesion formation at the site of placement. This mechanism of adhesion prevention, while effective locally, does not address the complex nature of adhesion formation which entails the interaction of biochemical events involved in inflammation, fibrinolysis and wound healing throughout the postoperative peritoneum.[5] Surgical trauma to the abdomen initiates a widespread inflammatory response in the peritoneum [23] that is associated with the recruitment and activation of inflammatory cells [22] and the secretion of proinflammatory mediators such as interleukin (IL)-1 and transforming growth factor (TGF)-β1 [23] This proinflammatory environment promotes the formation of a fibrin-rich matrix at the sites of peritoneal injury that leads to the

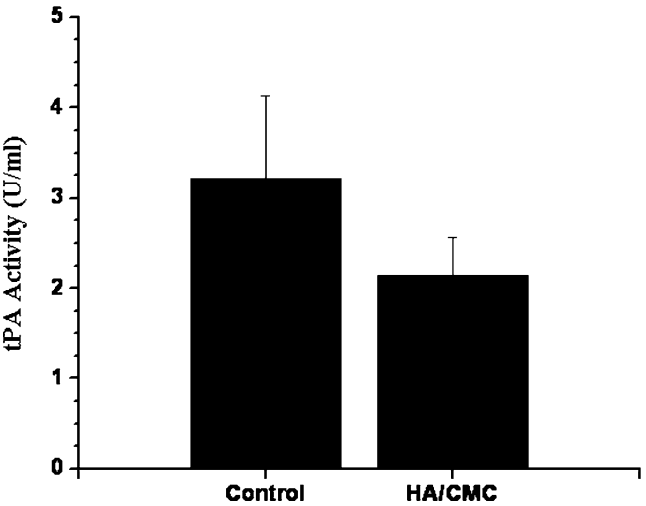

Figure 5 tPA activity in peritoneal fluid from operated control animals and animals 24 h after the bilateral application of hyaluronic acid/carboxymethylcellulose (HA/CMC) barrier. Data are expressed as the mean±SEM; $n=8$ per group.

formation of fibrinous adhesions and eventually permanent adhesions. While the physical separation of injured or healing peritoneal surfaces with an HA/CMC barrier prevents the fibrin matrix from forming the attachments that ultimately lead to adhesion formation, it does not appear to affect the generalized peritoneal inflammatory response that precipitates adhesion formation. It is difficult to predict all areas of the postsurgical peritoneum that will form adhesions, and in following this logic, it is equally difficult to prevent widespread adhesion formation using a physical barrier whose efficacy appears to be limited to the site of placement. A potential adjunct therapy to the use of HA/CMC barriers may be a pharmacologic approach which promotes the degradation of the fibrin matrix without interfering with wound healing.[26,29]

As mentioned earlier, the peritoneal fibrinolytic system has been shown to play a central role in the resolution of fibrinous adhesions following abdominal surgery.[20] The fibrin-rich matrix, which is the precursor to fibrous adhesions, is largely degraded by the proteolytic enzyme plasmin. Peritoneal plasmin is activated primarily by tPA, which is regulated, in turn, by plasminogen activator inhibitor (PAI)-1.[20] The relative levels of tPA and PAI-1 in the postoperative peritoneum regulate overall fibrinolytic activity, and consequently adhesion formation. Peritoneal fibrinolytic activity is reduced in patients following abdominal surgery due to either decreased tPA and/or increased in PAI-1.[30] The results of the present study and others [31] indicate that the antiadhesion effects of HA/CMC are not directly related to peritoneal fibrinolytic activity since the bilateral placement of HA/CMC for 24 h did not compromise peritoneal tPA activity. Instead, the physical barrier properties of the HA/CMC membrane appear to be primarily responsible for adhesion prevention.

We propose that the efficacy of current physical barrier methods of adhesion prevention could be substantially improved by the coadministration of pharmacologic or other agents that optimize the fibrinolytic activity within the peritoneum without causing significant hemorrhagic complication or impairing wound healing. Potential pharmacologic agents include neurokin-1 receptor antagonists,[29] statins,[32] and methylene blue [33] which we have been shown to reduce adhesion formation in a rat model, and to activate the peritoneal fibrinolytic system without compromising wound healing.[26,32]

Conclusion

Effective adhesion reduction by physical barriers appears to be limited to the site of application. Despite the presence of a bioresorbable membrane at predicted sites of adhesion formation in the peritoneal cavity, adhesions readily form to distal unprotected sites. While physical barriers are the most widely used method of adhesion prevention in patients and are effective in preventing postoperative adhesions where placed, pharmacologic agents do show significant promise, at least in animal models. Perhaps a combination of these two approaches, for example the development of a biodegradable barrier-based drug delivery system, may prove more effective than either approach alone in the prevention of adhesions. A pharmacologic agent that enhances peritoneal fibrinolysis but does not impede wound healing has the potential to be an ideal candidate. Ultimately, the goals of an improved method of adhesion prophylaxis would be improved effectiveness, reasonable cost, no adverse wound healing effects, and ease of handling and administration. Until a truly effective method to prevent adhesions is developed, further research examining the pathophysiological events that underlie adhesion formation is essential and undoubtedly will lead to improved methods of adhesion formation and ultimately successful postoperative adhesion prevention.

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Discussion

Margo Shoup, M.D. (Maywood, IL): I would like to congratulate the authors for trying to tackle a difficult problem that we all face with our patients with adhesion formation in a small bowel obstruction, and we really haven't made much headway in this in the last couple of decades. The authors in this paper attempt to study the effects of HA/CMC, or seprafilm, and neurokinin-1 receptor antagonist. The adhesions were measured at seven days postoperatively and placement of the buttons, and the Tpa was measured 24 hours after laparotomy. And we know that the synergistic effects of NK1RA and seprafilm is evident, but we are not really sure what is going on with the Tpa during all that. So I have a few questions for you.

Have you first looked at dose escalation studies with increasing NK1 receptor antagonists to evaluate the effects on Tpa, because this would clarify whether this is truly the mechanisms through which this is working. Also, you checked the Tpa levels 24 hours after surgery and, like I said, the adhesions at seven days. Have you looked at different time frames for both of these to see if there is more of a correlation? And at this point do you have any information on the status of the soluble seprafilm that is available in Europe, and if so, where do you think this may impact your study?
Thank you.

Rizal Lim, M.D. (Boston, MA): In terms of dose escalation of our antagonist, going back to the original parent compound, it is actually based off of a drug called ezlopitant. When we received this compound as a gift, the doses were actually based on the then maximum recommended dose of 25 mg/kg, which we used. But in earlier studies, as we started off with 5 mg/kg and then went to 10 mg/kg, we saw a progressive increase in adhesion prevention from those two doses.

In terms of the different time frames, looking at adhesions with this model specifically, our personal experience and data we have collected in the past have shown that when we look at adhesion formation beyond 7 days, we haven't really seen much of a difference in terms of severity. The same is true for tPA. In fact, what we have seen in previous studies is that tPA immediately post-op, at least within the rat, drops significantly and hits its nadir at approximately 24 hours and following that period of time begins to slowly rise back towards normal levels. So we chose that simply because it gives us a general idea of what the fibrinolytic activity within the abdomen is doing at its worst case scenario. We have also shown that giving the drug at 24 hours, we can alter that fibrinolytic activity.

And the final question, in terms of the soluble and gel forms of various barrier compounds, I am not firmly sure as to how far the various companies have progressed in terms of getting that approved within the U.S. But some of the implications which it may convey are that currently some of the biggest limitations of using HA/CMC barriers involve its actual application. It is a brittle, stiff material. It is difficult to use in certain cases such as laparoscopy, and I think that progressing to more of a gel type of device would improve its utility.

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An FDA Approved Neurokinin-1 Receptor Antagonist is Effective in Reducing Intraabdominal Adhesions when Administered Intraperitoneally, But Not Orally

Rizal Lim · Jonathan M. Morrill · Scott G. Prushik · Karen L. Reed · Adam C. Gower · Susan E. Leeman · Arthur F. Stucchi · James M. Becker

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R. Lim · J. M. Morrill · S. G. Prushik · K. L. Reed · A. C. Gower · A. F. Stucchi · J. M. Becker (✉)
Department of Surgery, Boston University School of Medicine,
88 East Newton St. C500,
Boston, MA 02118, USA
e-mail: james.becker@bmc.org

S. E. Leeman
Department of Pharmacology,
Boston University School of Medicine,
Boston, MA 02118, USA

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Dendritic Cells in Barrett's Esophagus and Esophageal Adenocarcinoma

Yuri V. Bobryshev · Dinh Tran · Murray C. Killingsworth · Michael Buckland · Reginald V. N. Lord

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Abstract
Background Like other premalignant conditions that develop in the presence of chronic inflammation, the development and progression of Barrett's esophagus is associated with the development of an immune response, but how this immune response is regulated is poorly understood. A comprehensive literature search failed to find any report of the presence of dendritic cells in Barrett's intestinal metaplasia and esophageal adenocarcinoma and this prompted our study.
Material and Methods We used immunohistochemical staining and electron microscopy to examine whether dendritic cells are present in Barrett's esophagus and esophageal adenocarcinoma. Immunohistochemical staining with CD83, a specific marker for dendritic cells, was performed on paraffin-embedded sections of Barrett's intestinal metaplasia (IM, $n=12$), dysplasia ($n=11$) and adenocarcinoma ($n=14$).
Results CD83+ cells were identified in the lamina propria surrounding intestinal type glands in Barrett's IM, dysplasia, and cancer tissues. Computerized quantitative analysis showed that the numbers of dendritic cells were significantly higher in cancer tissues. Double immunostaining with CD83, CD20, and CD3, and electron microscopy demonstrated that dendritic cells are present in Barrett's esophagus and form clusters with T cells and B cells directly within the lamina propria.
Conclusions These findings demonstrate that dendritic cells are present in Barrett's tissues, with a significant increase in density in adenocarcinoma compared to benign Barrett's esophagus. Dendritic cells may have a role in the pathogenesis and immunotherapy treatment of Barrett's esophagus and adenocarcinoma.

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Y. V. Bobryshev
Department of Surgery and Centre for Immunology,
St Vincent's Hospital, University of New South Wales,
Sydney, Australia

Y. V. Bobryshev
Faculty of Medicine, University of New South Wales,
Kensington, NSW 2052, Australia

D. Tran · M. Buckland
Division of Anatomical Pathology, St. Vincent's Hospital,
Sydney, Australia

M. C. Killingsworth
Department of Anatomical Pathology,
South Western Area Pathology Service,
Liverpool, NSW 2170, Australia

R. V. N. Lord (✉)
Department of Surgery and Centre for Immunology,
St Vincent's Hospital,
Suite 606, 438 Victoria Street,
Darlinghurst NSW 2010 Sydney, Australia
e-mail: rvlord@stvincents.com.au

Keywords Barrett's esophagus · Intestinal metaplasia · Esophageal neoplasms · CD83 · Dendritic cells · Inflammation

Introduction

Barrett's esophagus is the condition in which the normal squamous lining of the distal esophagus is replaced by a metaplastic columnar epithelium containing goblet cells (intestinal metaplasia, IM) in response to chronic severe gastro-esophageal reflux.[1–4] It is a multistage disease in which IM progresses in a minority of cases to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and eventually esophageal adenocarcinoma.[1–4] Despite significant improvements in medical and surgical oncology treatments, survival outcomes for patients with this cancer remain poor, with community 5-year survival rates less than 20%.[5] For reasons that are not fully known, but probably include an increase in Barrett's esophagus[6] and a causative association with the increased prevalence of overweight and obesity,[7,8] there has been a dramatic increase in the incidence of esophageal adenocarcinoma in many Western countries.[9,10] In the United States, for example, the rate of increase in esophageal adenocarcinoma incidence exceeds that of any other major cancer in the past 25 years, with a more than 600% increase.[9]

Components of the gastroesophageal refluxate are thought to include the injurious stimuli responsible for the accumulated genetic abnormalities present in Barrett's mucosa.[2,3,11] It has been reported that premalignant conditions that develop in the presence of chronic inflammation are often associated with the development of an immune response during the progression of the disease. How the immune responses are regulated is poorly understood,[12–15] but a marked increase has been reported in numbers of T cells and B cells in Barrett's oesophagus.[16] Antigen-specific T-cell activation is known to critically depend on the interactions of T-cell receptors with antigens presented by specialized antigen-presenting cells[17] including dendritic cells, a unique family of specialized antigen-presenting cells.[18–24]

Initially described in the skin by Langerhans in 1868, dendritic cells were identified as antigen-presenting cells in 1973 by the pioneering work of Steinman and Cohn.[25] Although macrophages, monocytes and B cells have traditionally been viewed as antigen-presenting cells, dendritic cells, which express high levels of both class I and class II major histocompatibility complex (MHC) molecules and co-stimulatory molecules, are now considered the principal initiators of immune responses by virtue of their unique ability to activate naive T cells.[18–24] Dendritic cells arise from a common CD34+ progenitor in the bone marrow and their development involves three stages, for which the terms precursor, immature, and mature, are commonly used.[18–24] Dendritic cell precursors exit the bone marrow and circulate via the bloodstream to reach their target tissues, taking up residence at sites of potential antigen entry.[18–24] In this stage, dendritic cells are present in essentially all tissues but are mostly concentrated along epithelial and body cavity surfaces. In these locations, dendritic cells continuously and efficiently sample the antigenic content of their microenvironment by phagocytosis or endocytosis.[18–24] Antigen is then processed intracellularly, being degraded into short peptides that are loaded onto nascent MHC for subsequent display on the cell surface. Cells with these properties are termed immature or processing dendritic cells as, in this stage, they are yet unable to stimulate T cells.[18–24] Processing dendritic cells usually exit the nonlymphoid tissues and migrate via the afferent lymph into the lymphoid tissues such as the spleen and lymph nodes, where dendritic cells then complete their maturation.[18–24] Maturation of dendritic cells involves the down-regulation of endocytotic activity and the up-regulation of adhesion molecules and antigen-presenting molecules. Once activated, dendritic cells migrate to the lymphoid tissues where they interact with T cells and B cells to initiate and shape the adaptive immune response.[18–24]

The involvement of dendritic cells in tumorigenesis has clinical importance. The infiltration of dendritic cells into some primary tumor types has been found to be associated with significantly improved patient survival and a reduced incidence of recurrent disease, indicating an important immune-regulating role for dendritic cells in the local tumor environment.[26–35] Furthermore, dendritic cells can be used to manipulate immune responses, including those for cancer immunotherapy.

We undertook this study after a comprehensive literature search failed to find any report of the presence of dendritic cells in Barrett's intestinal metaplasia and esophageal adenocarcinoma.

We now report that dendritic cells are present in Barrett's metaplasia, dysplasia, and adenocarcinoma, and speculate that dendritic cell-dependent lymphocyte activation might occur in this disease.

Material and Methods

Tissue Specimens and Routine Histology

Endoscopic biopsy or operative surgical specimens were obtained from 37 patients with Barrett's esophagus or esophageal adenocarcinoma. Barrett's esophagus was diagnosed by the presence of a macroscopic area of columnar-lined esophagus as well as microscopic intestinal metaplasia

with goblet cells. Material was collected in accordance with the principles outlined in the Declaration of Helsinki after approved by the Institutional Review Board of St. Vincent's Hospital, Sydney, and informed consent was obtained from each patient. Tissue specimens were processed by standard formalin fixation and paraffin embedding. Paraffin sections cut at 5–7 μm thickness were stained with Mayer's hematoxylin and eosin. After review by an experienced gastrointestinal pathologist, the specimens were classified as Barrett's intestinal metaplasia without dysplasia (IM, n=12), dysplasia (n=11), and adenocarcinoma (n=14).

Immunohistochemistry and Quantitative Analysis

Single and double immunostaining for CD83, an inducible glycoprotein belonging to the immunoglobulin superfamily,[36] was performed. CD83 is important in T-cell immunity mediated by dendritic cells and is the most specific dendritic cell marker.[36–40] For single immunostaining, after elimination of endogenous peroxidase activity by 3% H_2O_2, sections were preincubated with normal non-immune serum and then tested by avidin–biotin complex using a standard ABC immunoperoxidase method.[41] Anti-CD83 (Immunotech; cat no IM-2069) was used in a 1:50 dilution. After washing in Tris–phosphate buffered saline (TPBS), pH 7.6, the sections were incubated with a biotin-labeled secondary antibody, followed by a treatment with avidin–biotin complex (ELITE ABC, VECTOR PK61000). After washing in TPBS, brown staining was produced by 5-min treatment with 3,3'-diaminobenzidine (DAB). All the incubations were completed at room temperature. Archival lymph node sections were used for positive controls. For negative controls, the first antibodies were omitted or the sections were treated with an immunoglobulin fraction of non-immune goat serum as a substitute for the primary antibody. None of the negative control sections showed positive immune staining. Counterstaining was performed with Mayer's hematoxylin.

A computerized quantitative analysis of CD83 expression was carried out at ×400 magnification using the Image-Pro Plus image analysis program (Media Cybernetics, Bethesda, MD.). CD83 expression was measured in each section in at least seven randomly selected microscopic fields containing both CD83+ cells and epithelial glands. Statistical comparison of expression, measured in pixels per standard microscopic field (0.04 mm^2), was performed by t test using Prism® 4 (GraphPad Software, San Diego, CA.).

Double immunostaining with CD83/CD3 and CD83/CD20 was used to analyze the possible co-localization of dendritic

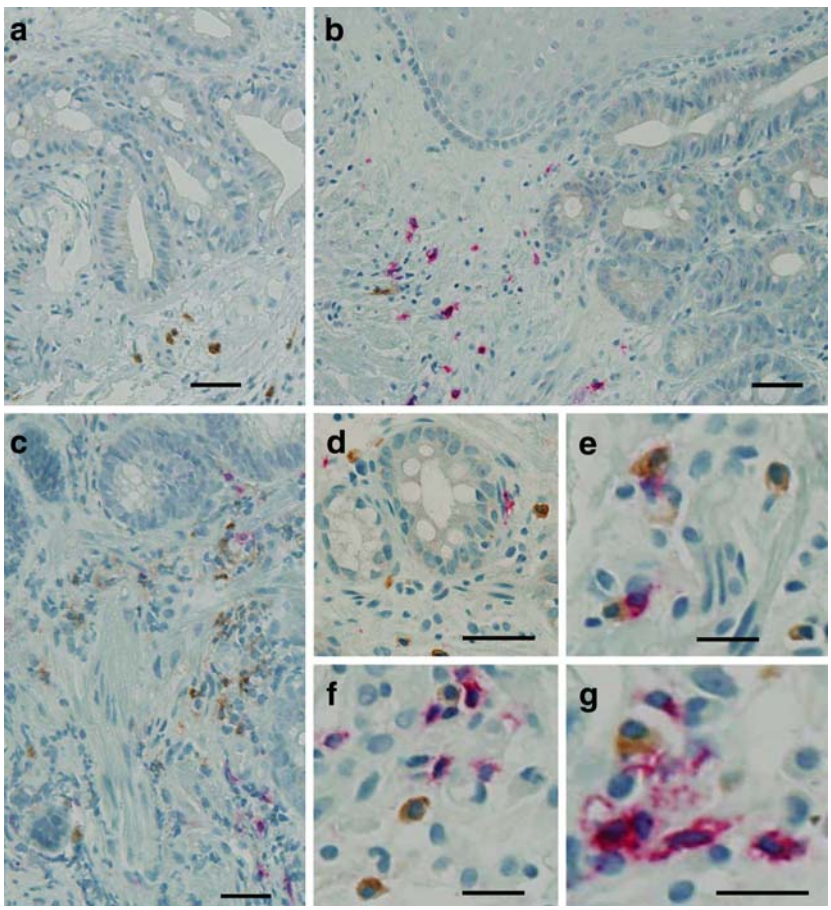

Figure 1 Typical patterns of distribution of CD83+dendritic cells in biopsy samples of Barrett's metaplasia (**A**–**G**). **A** Single ABC immunostaining showing the presence of dendritic cells (*brown*) in the lamina propria surrounding metaplastic glands. **B**–**G** Double immunostained sections showing the distribution of CD83+ dendritic cells and their association with lymphocytes. CD83 antigen was visualized using ABC immunoperoxidase reaction (brown reaction product) while CD20+ cells (**B**, **E**, **G**) and CD3+ cells (**C**, **D**, **F**) were visualized using a Fast red substrate kit (rose reaction product). Counterstaining with Mayer's hematoxylin. In (**E**–**G**), note dendritic cells clustering with lymphocytes. *Bars* = 100 μm (**A**–**D**) and 50 μm (**E**–**G**).

cells with lymphocytes, using previously reported methods.[37] In brief, after visualization of CD83 with the ABC substrate kit, sections were washed with 0.1M glycine-hydrochloric acid buffer, pH 2.2, and then incubated with anti-CD3 (Dako; cat no A0452; 1:100 dilution) or anti-CD20 antibody (Beckman-Coulter; cat no 1925; 1:50 dilution). After rinsing in TPBS, the sections were incubated with biotinylated secondary antibody and then with alkaline phosphatase-conjugated streptavidin (Dako) or with avidin–biotin complex (Dako). A combination of the peroxidase–anti-peroxidase (PAP) and alkaline phosphatase–anti-alkaline phosphatase (APAAP) techniques, with antigen visualization with DAB or Fast Red, was also used. Controls were as for single immunostaining.

Electron Microscopy

Fresh endoscopic biopsy specimens were fixed in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4), routinely processed and embedded in Spurr resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with the aid of a Morgagni 268D electron microscope. The electron microscopic identification of dendritic cells was carried out according to their distinctive ultrastructural features, which include the tubulovesicular system and atypical granules as previously used.[19, 42]

Results

CD83 expression was identified in all 12 specimens with Barrett's IM without dysplasia. The numbers of CD83+ dendritic cells varied markedly in different specimens and the cells were irregularly distributed throughout the lamina propria (Fig. 1A). The intensity of CD83 immunopositivity in individual cells varied notably as well, but in all specimens, dendritic cells located in close proximity to intestinal glands showed a lower intensity of immunopositivity than those located at a distance in areas of the lamina propria enriched by capillary networks. Double immunostaining utilizing combinations of anti-CD83, anti-CD20, and anti-CD3 antibodies revealed that all specimens contained various numbers of B cells (CD20+) and T cells (CD3+) and that dendritic cells, T- cells, and B-cells frequently formed clusters within the lamina propria (Fig. 1B–G).

CD83+ cells were present between dysplastic glands in all Barrett's dysplasia tissue specimens, often with a patchy distribution in the lamina propria (Fig. 2A,B) due to frequent clustering of dendritic cells (Fig. 2C). Direct contacts between dendritic cells and lymphocytes, including T and B cells, were also identified (Fig. 2C–E). When CD83+ dendritic cells were detected within inflammatory cell infiltrates in the lamina propria, each individual

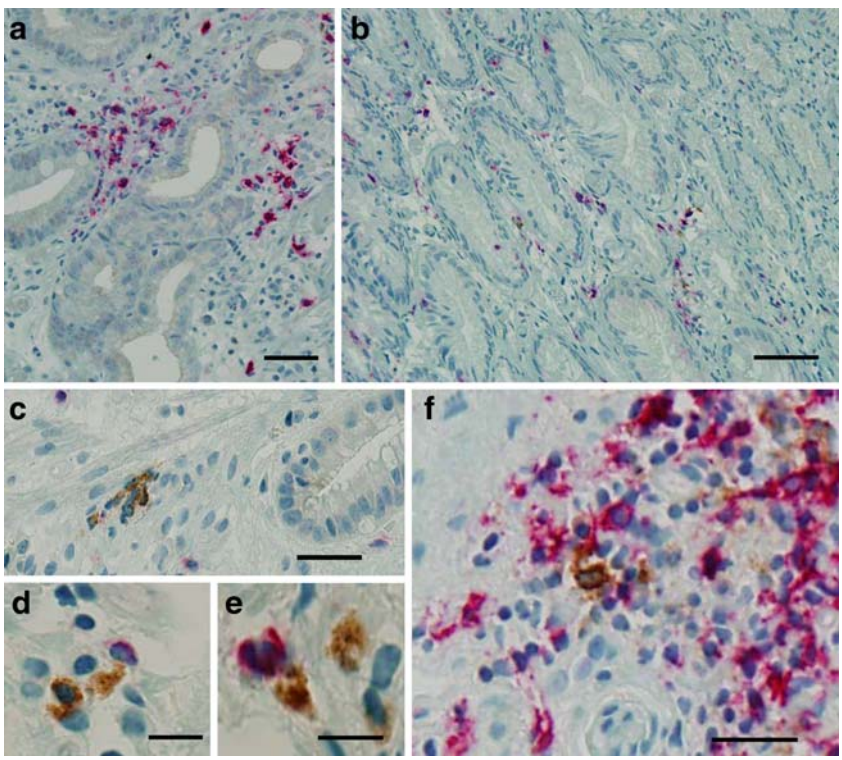

Figure 2 CD83+ dendritic cells in biopsy samples containing dysplastic changes in specialized intestinal type mucosa of Barrett's esophagus (**A**–**F**). CD83 antigen was visualized using ABC immunoperoxidase reaction (brown reaction product) while CD20+ cells (**A**, **E**, **F**) and CD3+ cells (**B**, **C**, **D**) were visualized using a Fast red substrate kit (rose reaction product). Counterstaining with Mayer's hematoxylin. In (**C**), note dendritic cells clustering with each other while in (**D**, **E**), close apposition between dendritic cells and lymphocytes is evident. **F** Association of dendritic cells with lymphocytes within an immune-inflammatory infiltrate in the lamina propria. *Bars*=100 μm (**A**, **B**) and 50 μm (**C**, **F**) and 25 μm (**D**, **E**).

dendritic cell seemed to cluster with several lymphocytes (Fig. 2F).

CD83+ dendritic cells were detected in all esophageal adenocarcinoma specimens. Similar to the pattern seen in the Barrett's dysplasia tissues, dendritic cells were distributed mosaically in clusters between distorted glands (Fig. 3A–E). Double immunostaining demonstrated direct contacts between dendritic cells and T and B cells in all specimens studied. Notably, contacts between CD83+ dendritic cells and lymphocytes were regularly seen in close proximity to capillaries (Fig. 3F) and dendritic cells were frequently observed within the lumen of capillaries forming networks within the lamina propria (Fig. 3G).

There was no significant difference between the mean CD83 expression in specimens of Barrett's IM (599±145) compared to Barrett's dysplasia tissues (730±167) on the computerized analysis (Fig. 4A). However, CD83 expression was significantly higher in adenocarcinoma specimens (1235±139) compared to either IM or dysplasia tissues (Fig. 4A). Figure 4 also shows the significantly higher CD83 expression in adenocarcinoma compared to non-adenocarcinoma Barrett's tissues (1235±139 vs 662+109; $p=0.0026$, all Student's t test).

The presence of dendritic cells was investigated further using electron microscopy. Cells with the typical appearance of dendritic cells in other tissues[19,42] were readily identified. The direct contacts between esophageal dendritic cells and lymphocyte-like cells as well as between dendritic cells and plasma cells were also detected (Figs. 5A–F, 6A–C. and 7A–D). Similar to dendritic cells elsewhere, dendritic cells in the esophagus were characterized by a cytoplasm of low electron density, which contained a tubulovesicular system

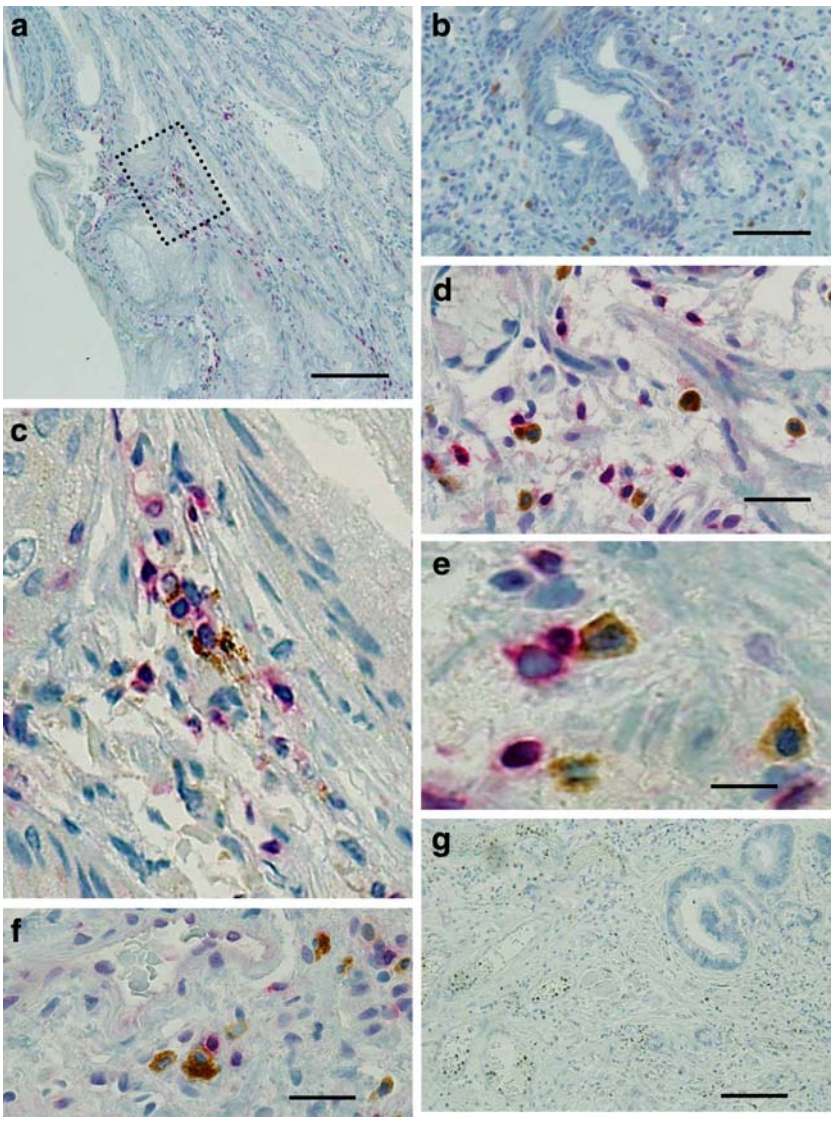

Figure 3 Patterns of distribution of CD83+ dendritic cells and their association with lymphocytes in esophageal adenocarcinoma tissue specimens (**A**–**G**). CD83 antigen was visualized using ABC immunoperoxidase reaction (brown reaction product) while CD3+ cells (**A**–**D**, **F**) and CD20 + cells (**E**) were visualized using a Fast red substrate kit (rose reaction product). Counterstaining with Mayer's hematoxylin. (**C**) is a detail of (**A**). In (**F**), note a contact of a dendritic cell with a lymphocyte in close proximity to a capillary. **G** Low magnification image showing the presence of dendritic cells within lumens of capillaries forming a network in an adenocarcinoma tissue specimen; dendritic cells are also seen around capillaries in the lamina propria. *Bars*=150 μm (**A**, **G**) and 100 μm (**B**), 50 μm (**D**, **F**) 25 μm (**E**).

unique to cells of the dendritic cell family (Figs. 5D, 6A–C, 7B,D). Atypical granules were present in some esophageal dendritic cells (Figs. 6A,B and 7A,B), but their cytoplasm lacked liposomes, rest bodies, or other organelles excluding the Golgi complex (Figs. 5A–F, 6A–C, and 7A–D). As with other dendritic cells, esophageal dendritic cells possessed long cell processes, the continuity of which with the dendritic cell body could be established in serial ultrathin sections (Figs. 6B and 7B). The cytoplasmic content of dendritic cell processes was limited either by granular and agranular material of medium and low electron density, respectively (Fig. 1B,E), or cisterns of the tubulovesicular system had developed in the cell processes (Figs. 6A,B and 7B). Through multiple cell processes, dendritic cells contacted T cell like cells (Fig. 1A–D) and plasma cells (Fig. 5E–F) or, alternatively, close apposition of the cell bodies of dendritic cells and lymphocytes was observed (Figs. 6A and 7A).

Histologically normal stratified squamous epithelium was present in some sections. There were only very rare CD83+ dendritic cells, and no glands, in the lamina propria underlying the normal squamous esophagus areas. Dendritic cells had a similar appearance in normal esophagus and Barrett's diseases.

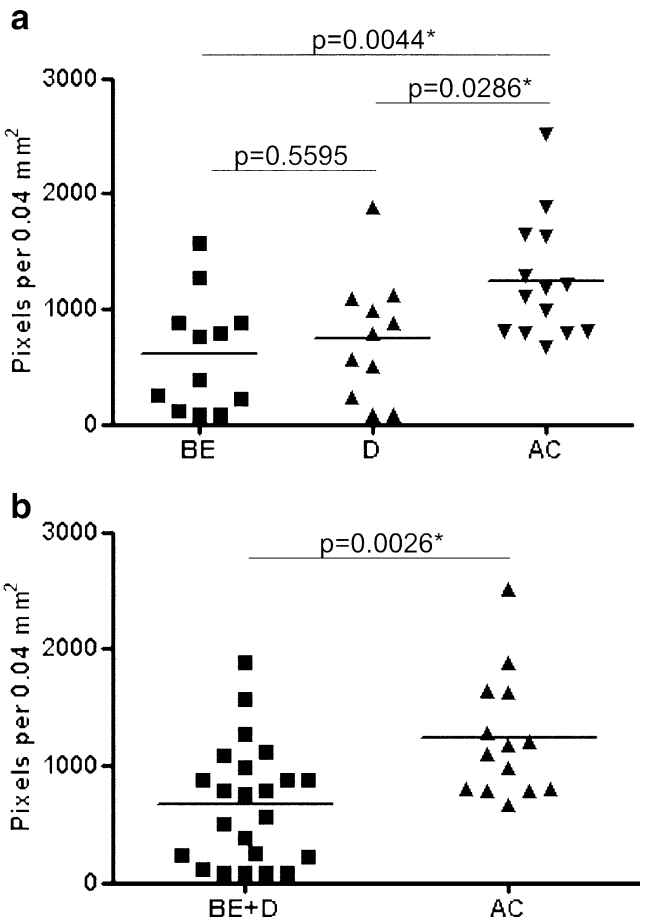

Figure 4 Expression of CD83 antigen in specialized intestinal type mucosa of Barrett's esophagus without dysplasia (*BE*), dysplasia (*D*) and adenocarcinoma (*AC*) evaluated as a number of pixel per standard field using a computerized quantitative analysis (**A**) (see "Material and methods" section). In (**B**), the expression of CD83 antigen in specimens without adenocarcinoma (*BE+D*) compared with that in adenocarcinoma specimens (*AC*).

Discussion

This study demonstrates, by both immunohistochemistry and electron microscopy, that dendritic cells reside in Barrett's esophagus and esophageal adenocarcinoma. The certainty of this finding is supported by the studies[36–40] reporting that CD83 is a specific marker for the identification of dendritic cells, by the typical dendritic cell appearance of the CD83+ cells found in Barrett's tissues, and, importantly, by the demonstration of the presence of cells with structural features unique to the dendritic cell family (tubulovesicular system and atypical granules) by electron microscopy.

The unambiguous identification of dendritic cells is essential because, to our knowledge, this is the first report of the presence of dendritic cells in Barrett's esophagus and esophageal adenocarcinoma. The novelty of this report is somewhat surprising in view of the interest in dendritic cell immunotherapy for cancers, including esophageal adenocarcinoma,[43] and indicates that there is a pressing need for further studies investigating the regulation of the immune response in this disease.

According to the concept of immune surveillance, the immune system is able to recognize and destroy a clone of transformed cells before the clone becomes cancer.[44] However, evidence from experimental and clinical observations shows that the immune system does not behave in this way for many tumor types.[44] Most tumor antigens are weakly immunogenic and the immune functions, such as the antigen-specific T-cell response initiated by professional antigen-presenting cells, and immune regulation mediated by regulatory cells often fail to operate adequately and thus fail to prevent tumor growth.[44–46] The importance of dendritic cells in immune surveillance suggests that infiltration of dendritic cells into tumors should have prognostic significance,[44–46] but this has not been a consistent finding. An increased infiltration of dendritic cells into esophageal squamous cell carcinoma and hepatocellular carcinoma is associated with good prognosis for patients with such cancers,[47–49] but there was no significant association with prognosis in two studies of patients with renal cell carcinoma, for example.[50–52] As an explanation for these variable findings, Mailliard et al.[53] suggest that

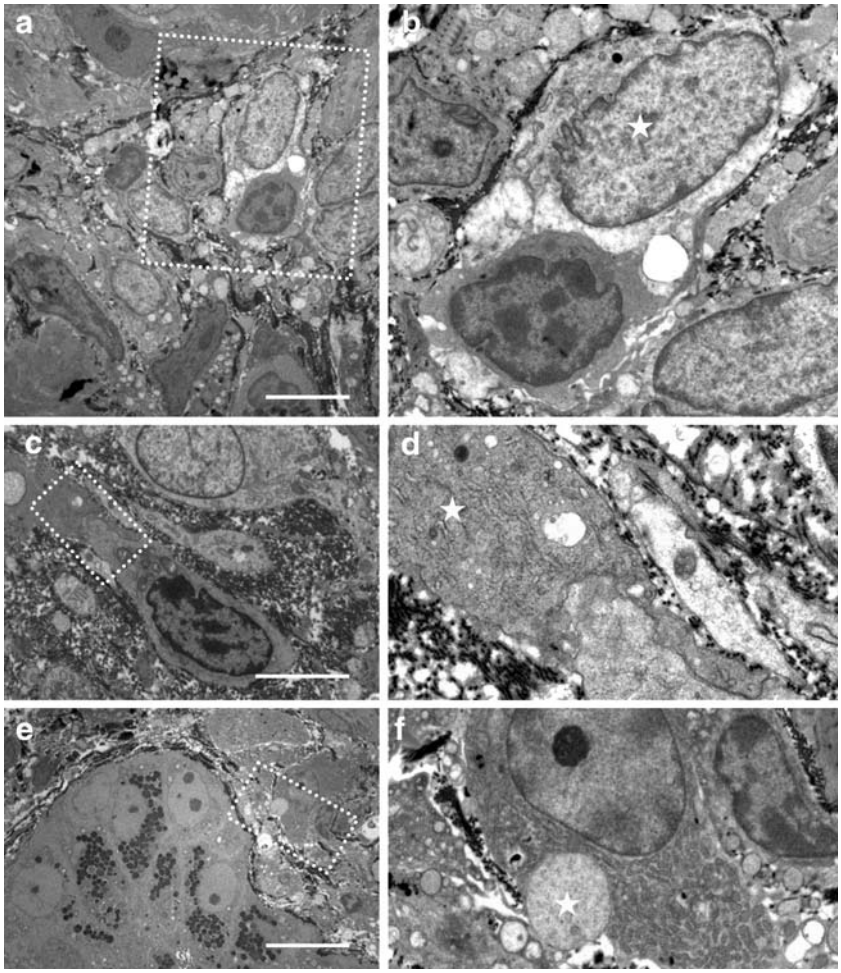

Figure 5 Electron micrographs showing close apposition between dendritic cells and T cells (**A**–**D**) as well as between a dendritic cell process and a plasma cell (**E**–**F**). (**B**) is a detail of (**A**); (**D**) is a detail of (**C**); (**F**) is a detail of (**E**). In (**B**, **D**, and **F**), dendritic cells are marked by stars. *Bars*=15 μm (**A**), 4 μm (**C**), and 20 μm (*E*).

infiltrating dendritic cells might promote T-cell survival or death, depending on their maturation stage and function.

We found significantly increased numbers of dendritic cells in adenocarcinoma compared to benign Barrett's tissues. Indeed, the density of dendritic cells in the cancer sections studied is among the highest, and perhaps the highest reported for any non-cultured tissue.[19] This descriptive study does not address whether dendritic cells may have a mechanistic role in the development and progression of Barrett's disease, but an involvement in local processes associated with the development of adenocarcinoma in the columnar epithelium is at least suggested. One mechanism for dendritic cell involvement is that, although the numbers of dendritic cells are increased, those residing in cancer tissues can be defective. Such a possibility is in agreement with the view that the defect of dendritic cells is one of the important factors leading to the immune escape of tumor growth.[54,55] A consequence of the maturation of defective dendritic cells can be a decrease in functionally competent dendritic cells.[54,55] Increased numbers of functionally incompetent dendritic cells can induce the tolerance of T cells, resulting in the tumor escaping from the surveillance of the immune system.[54,55] In renal cell carcinoma and prostate cancer, infiltrated dendritic cells have lower allostimulatory activity, while dendritic cells in the peripheral blood of patients with breast cancer express lower levels of both MHC II and co-stimulatory molecules.[54,55] Almand et al.[55] reported that despite that the increase in the numbers of dendritic cells in lymph nodes and peripheral blood, their ability to induce antigen-specific proliferation of autologous T cells is significantly decreased.

The present immunohistochemical analysis revealed that dendritic cells frequently contact both T cells and B cells in Barrett's esophagus and adenocarcinoma, and the electron microscopic analysis showed that dendritic cells form direct contacts with T cells through their long cellular processes. As found in other tissues,[19,42,56] the tubulovesicular system in the dendritic cell processes that contact T cells is highly hypertrophied, indicating dendritic cell activation. Although not the focus of this study, similar to the report by Moons et al.,[16] we found a large number of plasma cells in Barrett's esophagus, indicating that a significant humoral

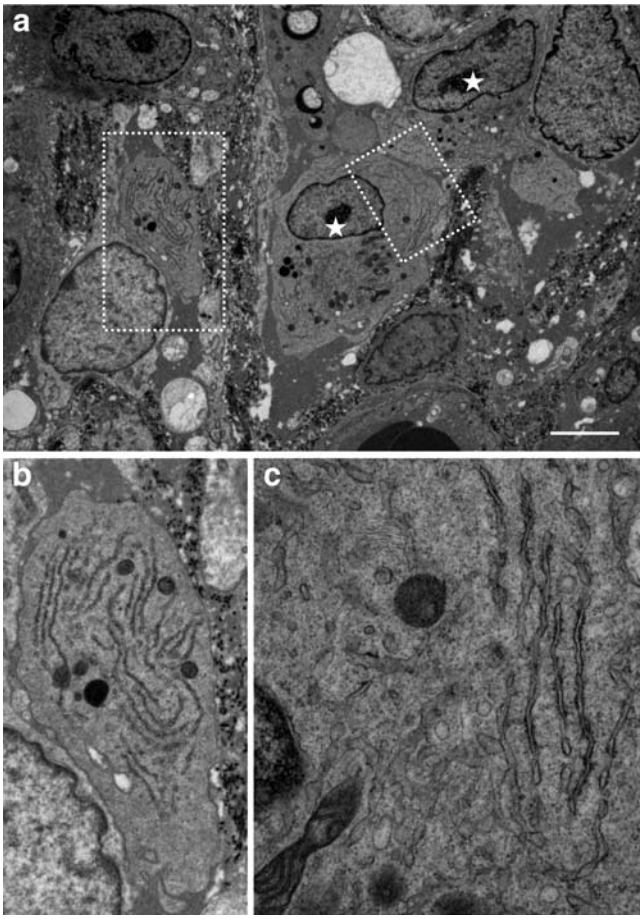

Figure 6 A group of dendritic cells (**A**) exhibiting highly hypertrophied tubulovesicular system in their cellular processes (**A**, **B**) and in the perinuclear cytoplasm (**A**, **C**). In (**A**), dendritic cells are marked by *stars*. An esophageal adenocarcinoma specimen. *Bar*=6 μm.

immune response is occurring locally within the lamina propria. Plasma cells with highly developed rough endoplasmic reticulum were seen in direct contact with dendritic cells, suggesting a role for dendritic cells in the regulation of immune reactions in esophageal pathology. Dendritic cells were found around and within capillaries in the lamina propria, further suggesting that esophageal dendritic cells might also migrate in the immune organs by means of the classical dendritic cell pathway.[18–24]

The identification of dendritic cells in Barrett's esophagus and esophageal adenocarcinoma has potential clinical importance. The remarkable ability of dendritic cells to elicit or diminish immune responses and the availability of sophisticated dendritic cell culture systems have stimulated the use of dendritic cells in cancer immunotherapy.[18–24,57] Recent achievements in loading dendritic cells with appropriate antigens have made it possible to produce in vitro dendritic cells with desirable properties.[57] Remarkable progress in the field of cellular vaccination has been achieved by means of genetic engineering of tolerogenic dendritic cells.[57] The very high density of dendritic cells in esophageal adenocarcinoma in this study supports efforts to develop dendritic cell immunotherapy for this cancer. The findings also suggest further studies on the prognostic significance of dendritic cell infiltration for progression to more advanced Barrett's stages and for the prognosis of patients with Barrett's cancer.

The scope of the present work was to investigate and report the presence of dendritic cells in Barrett's esophagus and esophageal adenocarcinoma and the observation that the number of dendritic cells in the cancers was significantly higher than in non-malignant Barrett's. Further studies are required in order to examine the prognostic value and functional characteristics of dendritic cells in this disease.

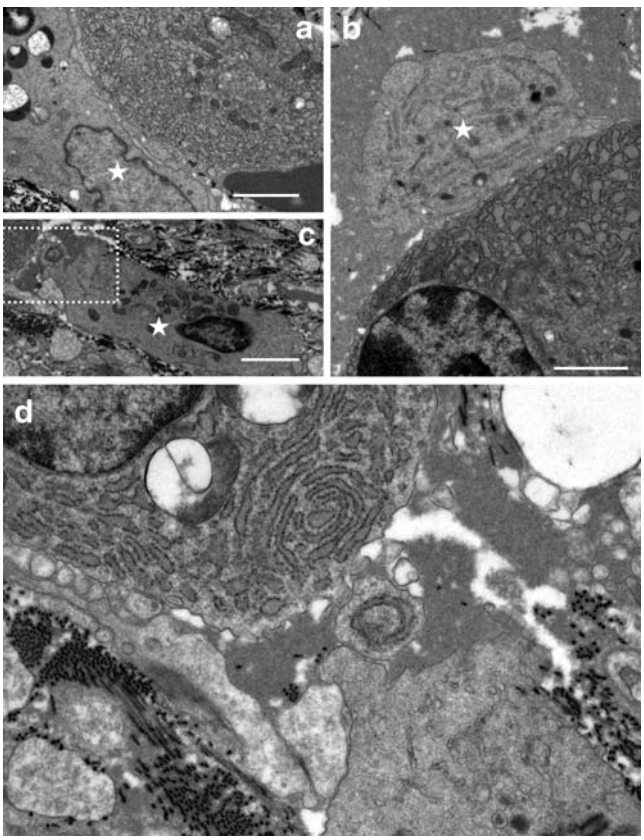

Figure 7 Direct contacts between dendritic cells and plasma cells (**A**–**D**). In (**A**–**C**), dendritic cells are marked by *stars*. Image (**A**) shows a close apposition of dendritic cell body to the plasma cell plasmalemma along a distance exceeding 3 μm while image (**B**) shows a contact of a dendritic cell process with the plasma cell body. In (**B**), note the presence of well-developed cisterns of the tubulovesicular system in a dendritic cell process while in (**A**), note the presence of atypical granules in the cytoplasm of the dendritic cell. **C**, **D** A direct contact between a dendritic cell microvillus and a short process of a plasma cell. (**D**) is a detail of (**C**). *Bars*=3 μm (**A**, **C**) and 2 μm (**B**).

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Recurrent Symptoms after Fundoplication with a Negative pH Study—Recurrent Reflux or Functional Heartburn?

Sarah K. Thompson · Wang Cai · Glyn G. Jamieson · Alison Y. Zhang · Jennifer C. Myers · Zoe E. Parr · David I. Watson · Jenny Persson · Gerald Holtmann · Peter G. Devitt

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Abstract
Introduction A small cohort of patients present after antireflux surgery complaining of recurrent heartburn. Over two thirds of these patients will have a negative 24-h pH study. The aim of our study is to determine whether these patients have an associated functional disorder or abnormal cytokine activity and to examine the reproducibility of pH testing.
Methods A prospective analysis was carried out on a cohort of patients who had undergone a fundoplication and postoperative pH testing for recurrent heartburn: group A—patients with recurrent heartburn and a negative 24-h pH study and group B (control group)—patients with recurrent heartburn and a positive pH study. Questionnaires, a blood sample, and repeat pH testing were completed.
Results Sixty-nine patients were identified. Group A's depression score (8.6±4.1) was significantly higher than group B's (5.9±4.2; $P=0.03$). Cytokine levels were similar in both groups. Forty-seven of 49 (96%) patients who underwent repeat pH testing had a negative study. Symptom-reflux correlation was highly significant ($P<0.001$).
Conclusion Some patients with recurrent heartburn and a negative pH study have associated functional or psychiatric comorbidities such as depression. Reproducibility of 24-h pH testing in these patients is excellent.

Keywords Laparoscopic fundoplication · Recurrent heartburn · Recurrent reflux · 24-h pH study · Antireflux surgery

S. K. Thompson · G. G. Jamieson · A. Y. Zhang · J. C. Myers · Z. E. Parr · P. G. Devitt
Discipline of Surgery, University of Adelaide, Adelaide, South Australia, Australia

J. Persson · G. Holtmann
Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, South Australia, Australia

W. Cai · D. I. Watson
Department of Surgery, Flinders University, Bedford Park, Adelaide, South Australia, Australia

S. K. Thompson (✉)
Department of Surgery, Royal Adelaide Hospital, Level 5, Eleanor Harrald Building, Adelaide, South Australia 5000, Australia
e-mail: sarah.thompson@adelaide.edu.au

Introduction

It is nearly two decades since the introduction of laparoscopic antireflux surgery and excellent 10-year outcomes have been reported recently, with success rates ranging up to 93%.[1–4] However, there are an equal number of studies that imply "surgical failure" rates of up to 30%.[5,6] The discrepancy between these numbers might reflect differences in definitions of surgical failure. Symptom control is often used as a marker of surgical outcome. However, "heartburn" is a subjective symptom that may not necessarily represent actual gastroesophageal reflux.

In a study published last year,[7] we found that only 26% of patients who had symptoms suggestive of recurrent reflux had abnormal esophageal acid exposure confirmed following 24-h pH monitoring. These results are consistent with three other studies[8–10] that also showed an abnormal pH study in only 23–39% of these patients. From these results, we concluded that 74% of the patients who had recommenced antisecretory medication after antireflux

surgery in our Department had commenced this medication unnecessarily.[7]

How can we explain this subset of patients' symptoms? Functional gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome are highly prevalent in Western populations. These disorders involve an increased visceral sensitivity characterized by a decreased threshold for the perception and sensation of pain for various stimuli such as gastric or colonic distension.[11] It is possible that some patients suffer from an "irritable esophagus" in a similar manner. The underlying mechanism for this altered perception is unclear; however, there is some evidence that abnormal inflammatory responses in the intestine may be relevant. A recent study has shown enhanced proinflammatory cytokine release in patients with diarrhea-prominent irritable bowel syndrome.[12] It is therefore possible that patients with recurrent symptoms but normal 24-h pH studies may have altered systemic cytokine release compared with patients with no symptoms and normal 24-h pH studies.

We therefore undertook a follow-up study to further investigate the small group of patients who had abnormal reflux before surgery, had a functioning fundoplication, and yet continued to have troublesome reflux symptoms. We wanted to determine: (1) whether these patients suffer from functional and/or psychiatric comorbidities, (2) if they have evidence of abnormal cytokine activity compared to patients with recurrent symptoms and abnormal esophageal acid exposure (i.e., true mechanical failure), and (3) if repeat pH testing is necessary for patients with recurrent heartburn after fundoplication and a normal postoperative 24-h pH study.

Materials and Methods

Patient Selection and Clinical Follow-up

Patients who underwent pH monitoring in the Department of Surgery at the Royal Adelaide Hospital after a fundoplication (open or laparoscopic) for "recurrent heartburn" were identified by comparing an esophageal function database of ambulatory 24-h pH study results, with a clinical surgical database which records prospective outcomes for all fundoplications performed by surgeons associated with the Departments of Surgery at the University of Adelaide and Flinders University in Adelaide, South Australia. Clinical outcomes were prospectively collected using a combination of postal questionnaires and telephone interviews at 3, 12 months, and yearly thereafter. Patients were included in this study if they had undergone a fundoplication (Nissen or partial) for gastroesophageal reflux disease, diagnosed before surgery by either an abnormal 24-h pH study (esophageal pH <4 for more than 4% of the study) and/or endoscopy with evidence of esophagitis (minimum Savary–Miller grade II). Patients were excluded if they had undergone postoperative pH monitoring to investigate dysphagia only. In addition to the information that was obtained from the databases, some medical records were reviewed as needed to assess clinic correspondence, endoscopy reports, and operation reports.

The patients identified were divided into two groups according to the result of the postoperative pH study: group A—patients with recurrent heartburn and a normal 24-h pH study (pH <4 for <4% of the study duration) and group B (control group)—patients with recurrent heartburn and an abnormal 24-h pH study (pH <4 for >4%). The routine investigations for group A patients were postoperative manometry, barium swallow, and upper endoscopy. Any patient with an abnormality which might have explained their recurrent symptoms (such as a paraesophageal hernia on barium swallow) was excluded from our study. Group B patients were all asymptomatic at the time of our study, as they had either undergone further revisional surgery, or achieved symptomatic control of their heartburn by using antisecretory medication.

Questionnaires

Information and an invitation to participate in this study were distributed by mail to patients who met the inclusion criteria. Responders were asked to complete three questionnaires to determine the impact of symptoms on quality of life (QOL), the nature of any pain, and the presence or absence of associated medical problems such as anxiety and/or depression. The questionnaires included:

1. A standardized assessment with regard to abdominal symptoms, as well as diagnostic and therapeutic measures since the relapse of symptoms
2. Hospital Anxiety and Depression Scale (HADS)[13]—a validated questionnaire assessing psychiatric comorbidities. Scores range from 0 to 21 for both the anxiety and depression subscales, with higher scores indicating greater depression or anxiety
3. Nepean Dyspepsia Index (NDI)[14]—a validated questionnaire to assess the impact of gastrointestinal symptoms on quality of life. The NDI QOL scores range from 0 to 99, with higher scores indicating a worsening quality of life

Blood Samples

All patients were asked to donate 40 ml of blood. Peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation, Ficoll-Hypaque (Sigma, Castle Hill, New South Wales, Australia). PBMC were

washed, resuspended to 1×10^6 cells/ml in medium (RPMI 1640 Gibco, Karlsruhe, Germany), and cultured in a final concentration of 1×10^6 cells/well for 24 h at 37°C and 5% carbon dioxide atmosphere. Cell-free conditioned medium was collected and stored at −20°C until assayed. Analysis of cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-10 were measured with commercially available ELISA kits (BD Biosciences, San Diego, CA, USA).

Repeat 24-h pH Study

Patients in group A were invited to have a further 24-h pH study. Acid-suppressing medications were discontinued for at least 5 days prior to this investigation. A single sensor pH probe (2.1 mm diameter; Medtronic Functional Diagnostics, Zinetics Inc, Utah, USA) was positioned 5 cm proximal to the upper margin of the lower esophageal sphincter. The position of the lower sphincter was identified by concurrent postoperative manometry in 66 of 69 patients (96%). In the three patients who refused postoperative manometry, the lower esophageal sphincter location was determined by triple pull-through of the pH probe using the "pH step-up" technique and positioned 6 cm above the level of change from gastric pH (<pH 4) to esophageal pH (>pH 4).[15,16] The pH probe was then left in situ for 24 h while the patient continued his/her normal activities. The data was collected on an ambulatory pH Digitrapper Mk III (Medtronic Functional Diagnostics, Denmark) and analyzed using EsopHogram ver2.01 (Polygram for Windows ver 2.04, Synectics Medical © 1996). A reflux event was determined to have occurred if the pH dropped below pH 4.0 for longer than 5 s. A cutoff value of pH <4 for more than 4% of the study duration was used to define "abnormal reflux". An electronic as well as handwritten diary was used to record symptoms, meals, and periods of supine posture. A symptom was considered to be associated with reflux when reflux was detected within a 2-min window before the onset of symptoms. A symptom index (SI) was calculated as the number of symptoms associated with reflux divided by the total number of symptoms, expressed as a percentage.

Statistical Analyses

GraphPad InStat (version 3.05; GraphPad Software Inc., San Diego, CA, USA) was used to perform the statistical analysis. Data were expressed as mean±standard deviation or number (percentage) as appropriate. Unpaired *t* test, Fisher's exact test, and the Mann–Whitney test were used where applicable to assess the significance of differences between the two study groups. Spearman's rank correlation test was used to assess the significance of correlations between depression scale and the NDI symptom score. Differences were considered to be significant at $P<0.05$. The protocol for this study was approved by the Research Ethics Committee of the Royal Adelaide Hospital.

Results

Out of 4,327 pH studies in the Royal Adelaide Hospital pH/manometry database and 1,948 individual patients who had undergone a laparoscopic fundoplication in our institution, 53 patients were identified with postoperative recurrent "heartburn" who met the inclusion criteria. The remaining 16 patients were referred to our clinic from other hospitals (23% of the total sample). The time interval between fundoplication and subsequent postoperative 24-h pH study testing ranged from 5 weeks to 21.5 years, with a mean time interval of 4.6 years.

Of these 69 patients, 54 (78%) patients had a normal 24-h pH study result (group A) and 15 (22%) patients had an abnormal result (group B). Patient characteristics are summarized in Table 1. The groups were comparable for age, sex, body mass index (BMI) values, preoperative 24-h pH study outcomes, and wrap type. However, the onset of recurrent "heartburn" symptoms following fundoplication occurred at 12 months (median 3 months) in group A patients compared with 39 months (median 30 months) in group B patients ($P\leq0.01$). This is consistent with our initial publication in which we found that patients in group A were significantly more likely to develop recurrent symptoms *within* 6 months of surgery compared to those in group B ($P<0.001$).[7]

Table 1 Demographic Data on 69 Patients with Recurrent Symptoms after Fundoplication

	Group A (n=54)	Group B (n=15)	P value
Age (years)	59±10.9	63±13.9	0.19
Gender (M/F)	26/28	5/10	0.39
BMI	27.6±6.0	25.6±4.2	0.23
Preoperative 24-h pH study[a]	13.3±13.7	15.0±9.1	0.73
Type of wrap	Partial[c] 12 (22.2%)	Partial[d] 4 (26.7%)	
	Nissen 42 (77.8%)	Nissen 11 (73.3%)	0.74
Technique	Lap 43	Lap 12	
	Lap-Open 3	Open 3	
	Open 8		
Time interval[b] (months)	Mean 12±19.5	Mean 39±37.9	0.009*
	Median 3	Median 30	

Group A—patients with recurrent heartburn and a negative 24-h pH study; group B (control group)—patients with recurrent heartburn and a positive pH study

[a] Group A n=33, group B n=9

[b] Group A n=28, group B n=8

[c] Ten anterior 90°; two anterior 180°

[d] Two anterior 90°; one anterior 180°

*$P<0.05$

Table 2 Symptom Profile of Patients with Recurrent Symptoms Before and After Antireflux Surgery

	Group A (n=54)		P value
	Preoperative	Postoperative	
Abdominal pain	23	19	0.55
Chest pain	25	20	0.44
Acid regurgitation	49	23	<0.0001*
Bloating	31	31	1.15
Hoarse voice	15	12	0.66
Food sticking	20	29	0.12
Heartburn	39	27	0.03*
Belching	25	24	1.0
Coughing	17	15	0.83
Sore throat	23	18	0.43
Shortness of breath	20	17	0.69

Group A—patients with recurrent heartburn and a negative 24-h pH study
*P<0.05

Patients' preoperative and postoperative symptoms for group A are listed in Table 2. Of note, there was a significant decrease after fundoplication of both complaints of "acid regurgitation" and "heartburn". At the time of initial presentation to the surgeon after fundoplication (with complaints of recurrent heartburn), 44 (81.5%) patients in group A and 12 (80%) patients in group B had recommenced antireflux medication. At the time of this study, 35 (65%) patients from group A and seven (47%) patients from group B were still taking antireflux medication. Fifteen patients (28%) in group A stated that antireflux medication was effective in controlling their recurrent symptoms compared to eight patients (53%, P=0.12) in group B.

The NDI symptom scores were abnormal in both groups (Table 3), suggesting impaired quality of life due to upper abdominal symptoms. Interestingly, quality of life scores of these two groups were not different. The Hospital Anxiety and Depression Scale scores are shown in Table 4. Group A's depression scores were significantly higher than Group B's. In contrast, anxiety scores were similar between both groups. There was a statistically significant correlation between the depression scores of the HADS and NDI symptom scores (r=0.28, P=0.02).

Table 3 Nepean Dyspepsia Index Scores in Patients with Recurrent Heartburn Following Antireflux Surgery

	Group A (n=54)	Group B (n=15)	P value
NDI symptom score	68.3±43.7	49.7±40.6	0.12
NDI quality of life score[a]	60.2±25.5	66.5±30.0	0.58

Group A—patients with recurrent heartburn and a negative 24-h pH study; group B (control group)—patients with recurrent heartburn and a positive pH study
[a] Group A n=52, group B n=12

Table 4 Hospital Anxiety and Depression Scale Scores in Patients with Recurrent Heartburn Following Antireflux Surgery

	Group A (n=54)	Group B (n=15)	P value
Anxiety	8.5±4.0	8.3±3.2	0.69
Depression	8.6±4.1	5.9±4.2	0.03*

Group A—patients with recurrent heartburn and a negative 24-h pH study; group B (control group)—patients with recurrent heartburn and a positive pH study
*P<0.05

Twenty-four of 54 (44%) patients with recurrent heartburn and a normal postoperative 24-h pH study (group A) and 12 of 15 (80%) of patients with recurrent heartburn and an abnormal pH study (group B) donated a blood sample. Cytokine levels are listed in Table 5. There were no significant differences in cytokine activity between groups.

Forty-nine of 54 (91%) in group A agreed to a second pH assessment. Forty-seven (96%) of these patients had a normal second postoperative pH study (pH <4 for <4% of the time). Thirty-six of the 47 patients (74%) with a normal pH study had a pH <4 for 1% or less of the study duration, and six of 47 (12%) had a pH <4 for between 1.1% and 2% of the study duration. Of the remaining seven patients, three had a pH <4 between 2.1% and 3% of the study duration, and four had a pH <4 for 3.1% to 4% of the study duration. Of note, five (11%) of 47 patients with a second normal pH study had a positive SI of >50%. Two patients (4%) had an abnormal result from their second postoperative pH study (esophageal acid exposure of 4.9% and 5.9%). However, neither of these two patients had a positive symptom index.

Discussion

There is good evidence that symptoms of recurrent heartburn after antireflux surgery are not a good indicator of abnormal esophageal acid exposure after antireflux

Table 5 Cytokine Levels in Patients with Recurrent Heartburn after Fundoplication

	Group A (n=24)	Group B (n=12)	P value
TNF-α	46.35±59.04	42.78±81.04	0.89
IL-1β	220.52±311.20	145.38±290.69	0.48
IL-6	2,426.86±3,310.61	1,489.87±2,787.14	0.39
IL-10	124.27±193.29	81.06±131.10	0.44

Group A—patients with recurrent heartburn and a negative 24-h pH study; group B (control group)—patients with recurrent heartburn and a positive pH study. All cytokine concentrations are pg/ml of conditioned medium

surgery. Four studies have tested patients with recurrent symptoms objectively, and from these papers, it is clear that a minority of patients (23–39%) have true recurrent reflux.[7–10] However, the reproducibility of 24-h pH monitoring is fundamental to this conclusion. A review of the literature demonstrates a concordance rate of only 73–80% with a second pH study in either normal controls or patients with esophagitis and/or gastroesophageal reflux disease symptoms,[17–19] but no studies have been reported in a postfundoplication group of patients. We therefore asked all study patients with a negative postoperative pH study to undergo a second 24-h pH test. Ninety-one percent consented to the procedure, and we found a 96% concordance rate with the previous test. Furthermore, similar to the findings we have reported previously, 74% of patients had a pH <4 for 1% or less of the time.[7]

It is of course possible that weakly acidic or weakly alkaline reflux events produced the heartburn symptoms in some of our patients. In our study, we did not perform combined pH-impedance studies to detect all reflux events, regardless of whether they were acidic, weakly acidic, weakly alkaline, or pure gas reflux, and this might mean we have missed some patients who truly had recurrent reflux.[20,21] However, Bredenoord et al. recently published a series of 14 patients studied with combined pH–impedance before and after fundoplication (two of whom had postoperative complaints of heartburn).[22] They found that antireflux surgery greatly reduces both acidic and weakly acidic reflux events and, to a lesser extent, gas reflux events. In particular, they describe a proportional decrease in both weakly acidic and acidic events and conclude that it is 'highly unlikely that patients who remain symptomatic after fundoplication despite a negative 24-h pH study suffer from reflux symptoms induced by weakly acidic reflux'.[22] These results were confirmed by Roman et al. (study to be discussed in greater detail below) for 23 symptomatic patients postfundoplication who found that a wrap is an effective antireflux barrier for *all types* of reflux events.[23] Hence, it is likely that the results of our current study remain valid, even in the absence of corroborating impedance study outcomes.

Five patients (11%) with recurrent heartburn and a negative pH study (group A) had symptoms of recurrent heartburn, a second normal pH study, and a SI of >50%. Based on a symptom association probability of >95%, Roman et al. (in the study described above) found a significant correlation between reflux events and symptoms in six patients in whom a negative 24-h pH study was found: acid reflux events in three patients and nonacid reflux in three.[23] Excluding the patients with nonacid reflux symptom correlation, we found a similar incidence of visceral sensitivity (11% vs. 13%). This suggests that some patients are aware of physiological reflux and might have a hypersensitive or "irritable" esophagus.[24,25] It is possible that a falsely elevated symptom index can occur in patients with frequent gastroesophageal reflux; however, the average number of reflux episodes in these five patients was low. Studies are ongoing to determine whether such patients have altered sensory receptors (increased perception of distension in the lower esophagus).[26] We found no evidence for altered systemic cytokine release in these patients.

In our initial study, we assessed nonsymptom-related parameters to determine whether there were any differences that could predict recurrent heartburn symptoms between the negative pH study group (group A) and the positive pH study group (group B). As with our previous study, in the present study, we found no significant differences in age, gender, body mass index, presurgery indications, and type of approach between the two groups. Patients with recurrent symptoms and a negative pH study (group A) had a significantly shorter time interval from operation to onset of recurrent symptoms, and their recurrent symptoms were less likely to involve acid regurgitation and heartburn.

Illness behavior questionnaires have been assessed previously in patients undergoing fundoplication in our center.[27–29] Our study focused on searching for an association between patients with recurrent symptoms plus a negative pH study and another well-recognized functional disorder, irritable bowel syndrome (IBS). The prevalence of IBS in patients with functional dyspepsia (as defined by the Rome II Criteria[30]) has been reported to be between 26% and 46%.[31] De Vries et al. reported 25% and 35% prevalence rates of functional dyspepsia and IBS, respectively, in patients with reflux.[32] They also examined the health-related quality of life in these different patient groups and came to the conclusion that a patient's quality of life is affected mainly by their concomitant functional disorders rather than by reflux itself. Our results support their findings. Patients with recurrent symptoms and a negative pH study (group A) had higher NDI[14] scores than those with a positive pH study (group B) although this did not reach statistical significance. This finding suggests that patients who return with recurrent symptoms and a negative pH study may be suffering from either undiagnosed functional dyspepsia or IBS and not a failure of their antireflux surgery.

Functional gastrointestinal disorders are commonly associated with other psychological disorders such as depression and anxiety, and symptoms of heartburn can be a manifestation of a psychological disorder.[33] We found significantly higher HADS[13] scores in group A patients (recurrent symptoms and negative pH study) compared to group B (recurrent reflux with positive pH study) patients. Moreover, there was a statistically significant correlation between the depression score and symptoms. Velanovich et

al. found that 93% of control patients were satisfied with their antireflux surgery compared to only 25% of patients with psychoemotional disorders or chronic pain syndromes.[34] Dissatisfaction in these patients was due to either persistent or new somatic complaints. In our study, we did not have baseline preoperative questionnaires to compare to the postoperative questionnaires. We cannot therefore determine if depression was present prior to surgery and led to the patients' perception of recurrent symptoms or whether their complaints of recurrent heartburn have led to the higher HADS scores. However, it is safe to conclude that fundoplication should be performed with caution in patients with psychiatric comorbidities such as depression or anxiety.

So, what is the best management for patients with recurrent heartburn symptoms after fundoplication? We would suggest that objective evidence of wrap failure should be obtained first with a 24-h pH study. We also confirm correct positioning of the wrap with a barium swallow, rule out any evidence of esophagitis with upper endoscopy, and include an esophageal manometry (for both accurate positioning of the pH catheter and to exclude motility problems). The minority of patients (23–39%) will have evidence of mechanical failure of their wrap (pH <4 for >4% of the time) and can be treated with either antireflux medication or revisional surgery. Patients with recurrent 'heartburn' and a negative pH test are a more challenging subset of patients. It is important to rule out other causes of 'heartburn' such as biliary colic, peptic ulcer disease, and cardiac causes. A repeat pH test to confirm initial results should be unnecessary in most patients.

The use of a gastric motility agent to increase gastric emptying is widely recommended in these patients, and some patients may obtain relief with either daily domperidone or the herbal medicine Iberogast.[35,36] In addition, one should consider whether these patients might benefit from a trial of antireflux medication even though our data suggests that this will be unsuccessful in the majority of patients. Bonatti et al. hypothesize that patients with atypical symptoms or a poor response to medical therapy prior to fundoplication may need both surgery and medication for control of their symptoms.[37] However, this is a speculative and controversial statement.

Finally, the surgeon should recognize that a fundoplication in patients with either IBS or psychiatric comorbidities may not achieve the same satisfaction rates compared to patients without these conditions. However, if dealing with a postoperative patient with either of these conditions, consider either a tricyclic antidepressant (to alter nociception) or psychological intervention.[38,39] The obvious association between depression and symptoms warrants properly designed prospective trials on the role of treatment with psychotropic medications such as tricyclic antidepressants for the control of pH-negative reflux symptoms.

Conclusion

There is a small group of patients who are proven to have abnormal reflux before surgery, who have an intact fundoplication, and yet continue to have heartburn symptoms for reasons that are not clear. We have determined that reproducibility of 24-h pH testing in these patients is excellent. Repeat 24-h pH testing is therefore unnecessary in most patients. Some patients have associated functional or psychiatric comorbidities such as IBS and depression. Gastric motility agents and/or tricyclic antidepressants may relieve symptoms. It is, however, clear that further research of this perplexing group of patients is required, specifically in patients who have a positive symptom correlation on their pH study and presumed "irritable esophagus".

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Laparoscopic Fundoplication in Patients with a Hypertensive Lower Esophageal Sphincter

Peter J. Lamb · Jennifer C. Myers · Sarah K. Thompson · Glyn G. Jamieson

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Abstract
Background A small proportion of patients evaluated with manometry prior to a fundoplication have a high-pressure lower esophageal sphincter (LES). This paper examines the outcome of laparoscopic fundoplication for these patients.
Material and Methods Between October 1991 and December 2006, 1,886 patients underwent primary laparoscopic fundoplication. Those with a high-pressure LES on preoperative manometry (LESP ≥30 mm Hg at end expiration) were identified from a prospective database. Long-term outcomes were determined using analogue symptom scores (0–10) for heartburn, dysphagia, and patient satisfaction and compared to those of a matched control group.
Results Thirty patients (1.6%), nine men and 21 women, median age 51 years, had a hypertensive LES (mean, 36 mmHg; range, 30–55). Median follow-up after fundoplication was 99 (12–182) months. These patients had similar mean symptom scores to 30 matched controls for heartburn (2.3 vs. 2.2, P=0.541), dysphagia (2.7 vs. 3.1, P=0.539), and satisfaction (7.4 vs. 7.6, P=0.546). Five patients required revision for dysphagia compared to no control patients (P=0.005). These patients had a higher preoperative dysphagia score (6.6 vs. 3.1, P=0.036).
Conclusion Laparoscopic fundoplication can be performed with good long-term results for patients with reflux and a hypertensive LES. However, those with preoperative dysphagia have a higher failure rate.

Keywords Lower esophageal sphincter · Antireflux surgery · Gastroesophageal reflux

Introduction

The finding on esophageal manometry of an isolated hypertensive lower esophageal sphincter (LES), in the absence of other motility abnormalities, has been recognized for many years.[1] Reports evaluating treatment for these patients are limited by small numbers and a lack of consistency in the manometric criteria used for its definition. Recent guidelines propose a pressure greater than 45 mm Hg in mid-respiration, with appropriate sphincter relaxation on swallowing and normal esophageal body motility.[2] However, most published studies evaluating the condition have used less stringent criteria and a lower cutoff, between 26 and 35 mm Hg, mid respiration.[3–5]

Chest pain and dysphagia were initially reported to be the most common symptoms associated with a hypertensive LES, and treatment was directed at reducing sphincter pressure, by medical or surgical techniques.[6,7] Although some patients fit this algorithm, it is now recognized that there is another group who present primarily with heartburn and are proven to have gastroesophageal reflux.[8,9] A hypertensive LES is diagnosed incidentally in these patients. This association appears paradoxical, as reflux is more commonly associated with a hypotensive, incompetent sphincter. The optimal surgical strategy is unclear, as there is concern about inducing dysphagia with a fundoplication, while a myotomy might worsen reflux. The aim of this study was to evaluate the long-term outcomes of laparoscopic fundoplication in these patients.

P. J. Lamb · J. C. Myers · S. K. Thompson · G. G. Jamieson (✉)
Discipline of Surgery, University of Adelaide,
Level 5, Eleanor Harrald Building, North Terrace,
Adelaide, South Australia 5005, Australia
e-mail: glyn.jamieson@adelaide.edu.au

Material and Methods

Between October 1991 and December 2006, all patients undergoing laparoscopic fundoplication for gastroesophageal reflux disease at the Royal Adelaide Hospital, Flinders Medical Centre or associated private hospitals with preoperative esophageal manometry were identified from a prospective database. Patients undergoing revisional antireflux surgery were excluded. Those undergoing repair of a large paraesophageal hernia (>50% of stomach in the chest) were also excluded, as the high-pressure zone might be due to extrinsic compression from adjacent tissues rather than the sphincter itself. The preoperative esophageal manometry was reviewed to identify patients with hypertensive LES. A control group of patients with non-hypertensive LES was also identified from the database. Study patients were individually matched to the next suitable patient in the database according to sex, age (within 5 years), year, and type of fundoplication and the degree of preoperative dysphagia.

Esophageal manometry was performed using a water perfused eight-channel esophageal motility catheter (Dentsleeve Pty. Ltd, Adelaide, Australia), introduced transnasally. The catheter comprised of six proximal channels spaced 5 cm apart, a 6-cm sleeve sensor, and one gastric channel. The LES was located by the station pull-through technique, and then the catheter was firmly taped with the sleeve sensor positioned across the sphincter for continuous measurement of LES pressure. Manometric measurements were recorded during a 5-min rest period, and a series of ten water swallows. We have previously demonstrated this technique to give reproducible measurements of LES pressure.[10] The criteria used to define the findings of esophageal manometry are given in Table 1. Basal LES pressure (millimeters of mercury) was the resting pressure sampled during the 5-min rest period (mean end expiratory pressure referenced to basal intragastric pressure). Traces for patients with a hypertensive LES were also retrospectively re-evaluated to determine the mean LES pressure at mid-respiration. The residual relaxation (nadir) pressure (millimeters of mercury) was the lowest pressure recorded during swallow-induced sphincter relaxation.

Laparoscopic fundoplication was offered to patients with proven reflux [endoscopic evidence of esophagitis or a positive 24-h pH study (pH <4 for >4% of study)], who were not controlled or unable to tolerate antireflux medication. The type of fundoplication performed was determined by surgeon preference in a similar manner in each group. For patients undergoing 360° fundoplication, a loose 2-cm-long wrap was constructed over a 52F intra-esophageal bougie, without routine division of the short gastric vessels. The techniques for 360° fundoplication, anterior 180°, and anterior 90 fundoplication have been described previously in detail.[11–13]

A follow-up was conducted using a standardized structured questionnaire, which evaluated symptom scores for heartburn, dysphagia for liquids and solids, and overall satisfaction with the outcome of surgery. This was administered by post or telephone by an independent nonclinical investigator preoperatively, 12 months following surgery, and annually thereafter until December 2007, allowing a minimum of 12 months follow-up. The presence or absence of heartburn and dysphagia was graded using an analogue scale from 0 to 10 (0–3, none or mild; 4–6, moderate; 7–10, severe). Patient satisfaction was also measured (0–3, unsatisfied; 4–6, satisfied; 7–10, highly satisfied). The most recent follow-up data was included for each patient, and outcomes were compared to those of the control group.

Statistical evaluation was performed using the Statistical Package for the Social Sciences (SPSS) statistical package (SPSS version 12, SPSS, Chicago IL, USA). Data are reported as the mean [95% confidence interval (CI)] or median (range). Chi-squared test was used to compare categorical data sets. Mann–Whitney *U* test was used for independent samples and Wilcoxon test was used for related samples to compare continuous data sets. Statistical significance was accepted at $P<0.05$.

Table 1 Criteria Used to Define the Findings of Preoperative Esophageal Manometry

Variable	Definition
Hypertensive LES	Median ≥30 mm Hg (end expiration)
Incomplete LES relaxation	Nadir ≥9 mm Hg
Reduced esophageal motility	<50% primary peristalsis
Hypertensive body contraction	>180 mm Hg (distal esophagus)

Results

Patients

Thirty of 1,886 patients (1.6%) undergoing laparoscopic fundoplication had a hypertensive LES on preoperative esophageal manometry. Patient demographics and manometry findings for 30 of these patients and their matched controls are given in Table 2. All 30 patients had confirmed gastroesophageal reflux, with endoscopic evidence of oesophagitis (22 patients), or a positive 24-h pH study (eight patients). No patient had endoscopic evidence of an esophageal stricture.

Table 2 Demographics and Preoperative Manometry Findings for Patients With Hypertensive LES (HLES) and a Matched Control Group

Variable	HLES (n=30)	Controls (n=30)	P value
Median age (years)	51 (20–79)	48 (18–75)	0.773
Sex (M/F)	9:21	9:21	Not applicable
360° fundoplication	20	20	Not applicable
Partial (anterior 90°, anterior 180°, posterior 270°)	10 (6, 3, 1)	10 (6, 3, 1)	
LES pressure (mm Hg)	36.4 (30–55)[a] 41.1(30–64)[b]	7.5 (0–23)[a]	<0.001
Nadir LES pressure (mm Hg)	5.9 (0–20)	1.2(0–8)	<0.001
Incomplete LES relaxation (n)	7[c]	0	<0.001
% Primary peristalsis	90 (20–100)	73 (0–100)	0.035
Reduced esophageal motility (n)	1	5	0.085
Distal esophageal contraction (mm Hg)	105 (28–189)	63 (0–165)	0.001
Hypertensive body contraction (n)	1	0	0.218

Data are given as mean (range) unless otherwise specified
[a] LES pressure at end expiration
[b] LES pressure at mid respiration
[c] 5 patients <75% relaxation

Follow-up Data

Outcome data were available for 29 of 30 patients (97%), with a median follow-up of 99 (range 12–182) months. One patient refused follow-up.

During follow-up, six patients with a hypertensive LES, all women, have required revisional antireflux surgery. One patient underwent revision for mechanical symptoms secondary to a paraesophageal hernia and was highly satisfied at the time of most recent follow-up. Five patients underwent revision for dysphagia; three required conversion to a partial fundoplication and two required surgery to widen a tight hiatus, after a 360° and an anterior 90° fundoplication, respectively. Four patients reported an improvement in dysphagia and were satisfied or highly satisfied with the outcome. There was a higher revision rate for dysphagia than in the control group (5/30 vs. 0/30, P=0.005).

The five patients undergoing revision for dysphagia originally had a higher mean preoperative dysphagia score for solids than other patients with a hypertensive LES [6.6 (4.5–8.7) vs. 3.1 (1.9–4.4), P=0.036]. Of 14 patients who reported moderate or severe preoperative dysphagia, seven required revision for dysphagia (five) or reported severe dysphagia (two) at their latest follow-up. The need for revision for dysphagia was not dependent on LES pressure (P=0.576), failure of LES relaxation (2/7 vs. 3/23, P= 0.334), or the type of fundoplication performed (4/20 360° vs. 1/10 partial, P=0.488),

The preoperative and most recent symptom and satisfaction scores for patients with a hypertensive LES and matched controls are given in Table 3. Patients with a hypertensive LES and the matched controls both reported a significant improvement in heartburn from preoperative levels but no change in dysphagia. Those with a hypertensive LES had similar preoperative and follow-up symptom scores to the matched controls for heartburn, dysphagia, and satisfaction. The seven patients with incomplete LES relaxation had similar symptom scores to other patients (Table 4).

Table 3 Analogue Symptom and Patient Satisfaction Scores for Patients with a Hypertensive LES (n=30), and Case Matched Controls (n=30)

Symptom	Preoperative		Latest follow up	
	HLES	Control	HLES	Control
Heartburn	7.7 (6.6–8.8)*	8.7 (7.9–9.4)**	2.3 (1.3–3.4)*	2.2 (1–3.3)**
Dysphagia (liquids)	1.9 (0.8–3.0)	2.2 (0.9–3.4)	1.6 (0.6–2.5)	1.0 (0.2–1.8)
Dysphagia (solids)	3.3 (2.0–4.6)	3.6 (2.1–5.0)	2.7 (1.5–3.9)	3.1 (2.0–4.3)
Satisfaction			7.4 (6.2–8.7)	7.6 (6.7–8.5)

Data are given as mean (95% confidence interval). No tests for significance between groups at comparable time intervals were significant. The only significant difference in symptom score between preoperative and latest follow up was for heartburn
*P<0.001, **P<0.001

Table 4 Influence of the Degree of LOS Relaxation on Outcome for Patients with a Hypertensive LOS

Symptom	LOS relaxation	
	Normal (n=23)	Incomplete[a] (n=7)
Heartburn	2.3 (1.0–3.7)	2.4 (0.6–4.3)
Dysphagia (liquid)	1.8 (0.5–3.0)	0.9 (0–2.0)
Dysphagia (solid)	3.0 (1.4–4.6)	1.7 (0–3.4)
Satisfaction	7.2 (5.6–8.7)	8.1 (5.8–10)

Data are given as mean (95% confidence interval). No tests for significance between groups were significant (P>0.05)
[a] Nadir LOS pressure ≥9 mm Hg

Discussion

This study confirms that some patients with proven reflux have a high pressure LES[3–5,14] albeit accounting for only 1.6% of those undergoing fundoplication. The definition used for a hypertensive LES (mean, ≥30 mm Hg end expiration) was similar to published guidelines,[2] as this translated to a mean pressure of 41 mm Hg in mid-respiration, when traces were specifically re-analyzed in this fashion. The study is unable to determine the proportion of patients with a hypertensive LES who present with reflux symptoms, rather than dysphagia, as it included only patients who underwent fundoplication for reflux. However, it is worth noting that no patient has undergone a myotomy for dysphagia and an isolated hypertensive LES, since the laparoscopic approach was introduced to the unit in 1992.

Small studies have previously reported encouraging results after fundoplication in patients with reflux and a hypertensive LES, with good outcomes for 11 of 12 patients,[3] six of six patients,[5] and three of four patients,[14] respectively. In our study, the long-term outcome was encouraging, with a significant reduction in heartburn symptoms and high levels of patient satisfaction, similar to a matched control group. However, importantly, a higher proportion of patients with a hypertensive LES required revisional surgery for dysphagia (five of 30). Troublesome dysphagia has always been the main perceived risk of performing a fundoplication for such patients. A relationship between increasing LES pressure and the risk of developing postoperative dysphagia following laparoscopic Nissen fundoplication has previously been reported.[15]

When risk factors for developing dysphagia were evaluated, these patients were found to have had a higher dysphagia score prior to their original fundoplication. The finding of a less satisfactory outcome for patients with preoperative dysphagia differed from Tambankar's study, which reported resolution of chest pain and dysphagia for all patients with a hypertensive LES and reflux following Nissen fundoplication.[4] The reason for this is unclear, although they used a lower cutoff to define a hypertensive LES (26 mm Hg mid-respiration). In an attempt to isolate the impact of a hypertensive LES, our control group was matched for preoperative dysphagia. This is a potential limitation of the study, as control patients had poorer peristaltic function, and neither may have represented a 'standard' group undergoing fundoplication. Certainly, the preoperative dysphagia scores for both groups were higher, and satisfaction scores were lower than previously reported cohorts from our unit.[16]

Postoperative dysphagia did not appear to be a result of including patients with other motility disorders. Esophageal manometry demonstrated that only a minority of patients with reflux and a hypertensive LES had other motility abnormalities. Those with incomplete sphincter relaxation underwent fundoplication provided that they retained peristaltic function and did not meet criteria for the diagnosis of achalasia.[2] This appeared to be an appropriate strategy, as we found no relationship between incomplete sphincter relaxation and postoperative dysphagia, and no patients subsequently developed criteria for a diagnosis of achalasia during follow-up. Similarly, Tambankar reported good results in 12 patients, which included six with incomplete sphincter relaxation and five with hypertensive body contractions.[4]

Conclusion

Patients with reflux and a hypertensive LES are clearly a heterogeneous group. Our findings suggest that for patients presenting with proven reflux and minimal dysphagia, the results of fundoplication are not influenced by the presence of a hypertensive LES. The surgeon can therefore be reassured that the incidental finding of a hypertensive LES on preoperative manometry can be ignored in these patients. Those with reflux and severe preoperative dysphagia appear to be at a higher risk of failure due to postoperative dysphagia, although this finding is based on a small number of patients due to the rarity of the condition. One strategy to improve outcome for these patients might be to perform a partial fundoplication. Although this seems logical and revision to a partial fundoplication improved our patients' dysphagia, we do not have sufficient numbers formally addressing this question. The alternative is to perform a lower esophageal myotomy combined with partial fundoplication, as recommended for patients with dysphagia and a hypertensive LES, in the absence of reflux.[4] This approach should certainly be considered for patients whose primary indication for surgery is dysphagia and who have minimal or well-controlled reflux symptoms.

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Geranylgeranylacetone Prevents Acute Liver Damage after Massive Hepatectomy in Rats through Suppression of a CXC Chemokine GRO1 and Induction of Heat Shock Proteins

Hirofumi Kanemura · Kenji Kusumoto · Hidenori Miyake · Seiki Tashiro · Kazuhito Rokutan · Mitsuo Shimada

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Abstract
Background and Methods Acute liver failure after massive hepatectomy remains a challenging problem. In this study, using a microarray designed to monitor the side effects of drugs, we examined changes in gene expression in the remnant liver during the 24 h after hepatectomy and the effects of a nontoxic heat shock protein (HSP) 70 inducer, geranylgeranylacetone (GGA), after 90% hepatectomy in rats.
Results A single oral administration of 100 mg/kg GGA significantly suppressed the release of aminotransferases and improved survival compared with vehicle administration. The hepatectomy upregulated 74 genes and downregulated 95. Interestingly, ten cytokine genes were upregulated, while no cytokine-related gene was downregulated. Among the ten cytokine genes, a potent chemoattractant for neutrophils, GRO1, was most rapidly and markedly upregulated after 90% hepatectomy. GGA effectively suppressed the up-regulation of *GRO1* messenger ribonucleic acid, and this was validated by Northern hybridization. Microarray and immunoblot analyses showed that, in addition to HSP70 and HSP27, GGA preferentially induced an endoplasmic reticulum chaperone, BIP.
Conclusion Considering hemodynamic and metabolic overloading as a primary cause of acute lever failure, the ER stress response enhanced by GGA may also play an important role in the prevention of overload-induced liver damage.

Keywords Massive hepatectomy · Acute liver damage · Geranylgeranylacetone · Heat shock proteins

H. Kanemura · H. Miyake · S. Tashiro · M. Shimada (✉)
Department of Digestive and Pediatric Surgery,
Institute of Health Biosciences,
The University of Tokushima Graduate School,
3-18-15 Kuramoto-cho,
Tokushima 770-8503, Japan
e-mail: mshimada@clin.med.tokushima-u.ac.jp

K. Kusumoto · K. Rokutan
Department of Stress Science, Institute of Health Biosciences,
The University of Tokushima Graduate School,
Tokushima 770-8503, Japan

Introduction

Hepatectomy is one of the most effective means of managing primary and metastatic liver tumors. To reduce mortality and morbidity after extended hepatectomy, post-operative liver failure is one of the most intensive problems.[1,2] The liver failure has been considered to be caused by many factors, including disturbances of hepatic microcirculation,[3] endotoxemia,[3–5] overproduction of inflammatory cytokines,[6–8] reactive oxygen intermediates,[9] and apoptosis.[10]

Heat shock proteins (HSPs) are molecular chaperones that are essential for the quality control of intracellular proteins.[11] In response to various types of stressors, mammalian cells induce HSPs and acquire tolerance against them. A stress-inducible 70-kDa HSP (HSP70) is one of the best-known endogenous factors protecting cells and tissues against injuries under various pathologic conditions.[12,13]

Geranylgeranylacetone (GGA), which is used as an antiulcer drug in Japan, is now known as a nontoxic HSP70 inducer with protective actions on hepatocytes.[14] It has been shown that pretreatment of rats with GGA could suppress ischemia/reperfusion injury of the liver[15] and improve the survival rate of rats undergoing massive hepatectomy[16] or liver transplantation.[17] In a previous study,[16] we found that 40% of rats given a single preadministration of GGA could survive, even after 95% hepatectomy, a condition causing 100% lethality within 60 h.[16] Even in such cases, GGA could preserve an HSP70-inducing capability in the remnant liver. However, 95% hepatectomy is too severe to allow a study of the molecular mechanism underlying actions of GGA, since more than half of GGA-pretreated rats still died within 100 h of the hepatectomy.[16]

In the present study, to elucidate the cellular pathways and mechanisms involved in the pharmacological action of GGA, gene expression profiles were examined after 90% hepatectomy using a complimentary deoxyribonucleic acid (cDNA) microarray specifically designed to monitor the side effects of drugs.

Material and Methods

Animals and Reagents

All animals were treated in accordance with the National Institute of Health Guide for the Care and Use of Laboratory, and all experiments and procedures were approved by the Animal Care Committee of the University of Tokushima. Male Wister rats weighing 230–260 g were obtained from Charles River Japan (Kanagawa, Japan). All animals were kept in identical housing units in a room maintained at 23°C on a 12-h light–dark cycle and fed standard rat chow (Oriental Yeast, Tokyo, Japan) and tap water ad libitum until the day before the operation. α-Tocophenol and GGA supplemented with 2 μg/mL α-tocophenol as an antioxidant were provided by Eisai (Tokyo, Japan).

Surgical Operation

After an overnight fast, GGA (100 mg/kg body weight; as an emulsion with 5% gum arabic and 0.004% α-tocophenol) or vehicle (5% gum arabic emulsion with 0.004% α-tocophenol) was intragastrically administrated into rats 4 h prior to the operation, as previously described.[16] After rats were anesthetized with diethylether, 90% hepatectomy was performed as described previously.[16] Briefly, the left, median, right-upper, and right-lower lobes were removed, leaving the caudate lobes, which represent 10–11% of the original liver mass.

Liver specimens and blood samples were collected after laparotomy and exsanguinations under deep anesthesia immediately before (0) and 4, 8, 12, and 24 h after the operation. After the wet weights of removed livers were measured, small pieces of liver tissue (about 100 mg) were immediately stored in an RNeasy stabilization kit (Qiagen, Hilden, Germany) at 4°C overnight and then stored at −80°C. Sera were immediately separated, and the activities of alanine (ALT) and aspartate (AST) aminotransferases were measured as described previously.[16]

Microarray Analysis

Using an RNeasy total ribonucleic acid (RNA) isolation kit (Qiagen), RNA was prepared from the liver tissues collected from both vehicle- and GGA-pretreated rats before (0) and 4, 8, 12, and 24 h after the operation. An equal amount of RNA prepared from each of three vehicle- or three GGA-pretreated rats at each time point was mixed and used for microarray analysis. Contaminating DNA was removed using a DNase kit (Qiagen). The quality of purified RNA was examined using an Agilent 2100 Bioanalyzer with an RNA 6000 Nano Labchip kit (Agilent Technologies, Palo Alto, CA, USA). Five micrograms of total RNA was first reverse-transcribed with an oligo dT primer-conjugating T7 sequence. First-strand cDNA complementary to poly (A) RNA was amplified using a MEGAscript T7 in vitro RNA transcription kit (Applied Biosystems, Foster City, CA, USA). Amplified RNA (5 μg) was reverse-transcribed using random hexamers and amino-allyl-deoxyuridine triphosphate. The synthesized cDNA was labeled by reaction with dyes (NHS-ester Cy5 or Cy3; Amersham Biosciences). To examine the effect of 90% hepatectomy, Cy5-labeled cDNAs prepared from vehicle-pretreated rats at the indicated time points after the surgery were mixed with the equivalent amount of Cy3-labeled cDNAs obtained from vehicle-pretreated rats before the operation (reference). To examine the pharmacological action of GGA, Cy5 cDNAs prepared from GGA-pretreated rats before or at the indicated times after the operation were mixed with an equivalent amount of Cy3 cDNAs prepared from vehicle-pretreated rats at the same time points (reference). The mixture was applied to a cDNA microarray carrying 1,096 cDNA probes (see http://www.hitachi.co.jp/LS/ for the full list of genes). Hybridization was performed at 62°C for 12 h. After washing, fluorescence intensity at each spot was assayed using a scanner (ScanArray 5000; GSI-Lumonics, Billerica, MA, USA). The intensities of Cy5 and Cy3 were quantified and analyzed by subtracting backgrounds, using QuantArray software (GSI-Lumonics). After global normalization, the values for duplicate cDNA probes were averaged. Then, we selected 640 genes with fluorescence intensities higher than a cutoff value of 500

under either Cy5 or Cy3 conditions among all samples. In order to consider the criteria of this microarray chip, we performed comparative experiments by hybridizing the same two samples on a microarray chip after labeling with Cy5 and Cy3 (self–self test) and decided that cutoff values of higher than 500 were sufficient for analysis. Considering a mean coefficient of variation of less than 20% of the microarray and sample numbers, we determined significantly responsive genes to be those whose messenger RNA (mRNA) levels differed by greater than twofold compared with the reference.

Reverse Transcription PCR and Northern Hybridization

Total RNA (1 μg) prepared as described above was reverse-transcribed using MuLV reverse transcriptase (Promega). Polymerase chain reaction (PCR) was performed using a *Taq* polymerase Promega PCR Kit in accordance with the manufacturer's protocol. The sequences of the primer sets used were as follows: *GRO1*, 5′-ATTTAACGATGTGGA TGCGTTTC-3′ (sense) and 5′-ACACGATCCCAGAC TCTCATCTC-3′ (antisense); *glyceraldehyde-3-phosphate dehydrogenase* (*GAPDH*), 5′-ACCACAGTCCATGCCAT CAC-3′ (sense) and 5′-AGGTGGTGGGACAACGACAT-3′ (antisense). Each PCR reaction was performed according to the manufacturer's protocol (Promega) using an ABI 7500 system (Applied Biosystems). The optimal number of PCR cycles was determined to be 28 by checking linear amplification at a variable number of cycles (from 20 to 35). *GAPDH* was used as an internal quantity control. PCR products were sequenced with a DNA sequencer and confirmed to be the corresponding cDNA fragments.

To validate the semiquantitative measurements by reverse transcription (RT)-PCR, *GRO1* mRNA levels were measured by Northern blot analysis. Briefly, 30 μg of denatured total RNA was electrophoresed in a 1% agarose formaldehyde gel and then transferred to a Hybond-N^+ nylon membrane (Amersham Pharmacia, Piscataway, NJ, USA). The membrane was hybridized with a ^{32}P-labeled cDNA probe for rat *GRO1* or *GAPDH*. The hybridized signals were detected by autoradiography.

Western Blot Analysis

Liver proteins were prepared and subjected to immunoblot analysis, as previously described,[16] using a 1:1,000 dilution of a mouse monoclonal antibody against BIP (Santa Cruz Biotechnology, Santa Cruz, CA, USA), a mouse monoclonal antibody against HSP70 (Santa Cruz Biotechnology), or a rabbit polyclonal antibody against HSP27 (Santa Cruz Biotechnology). Bound antibodies were detected using an enhanced chemiluminescence Western blotting detection kit (Amersham Pharmacia).

Statistical Analysis

Results are reported as means ± SD. Analysis of variance (ANOVA) and Scheffé's test were used to determine statistically significant differences. Differences were considered significant if $P<0.05$.

Results

Effects of GGA on Acute Liver Injury and Survival After 90% Hepatectomy

In a previous study,[16] we examined the dose-dependent effects of GGA (from 1 to 200 mg/kg) on survival after 95% hepatectomy in rats and determined 100 mg/kg to be the optimal dose for a single oral administration at 4 h prior to the operation.

In this study, we first tested whether GGA (100 mg/kg) was similarly effective in the case of 90% hepatectomy. As shown in Fig. 1a,b, a single oral administration of 100 mg/kg GGA at 4 h before 90% hepatectomy significantly suppressed elevations in serum ALT and AST levels within 24 h after

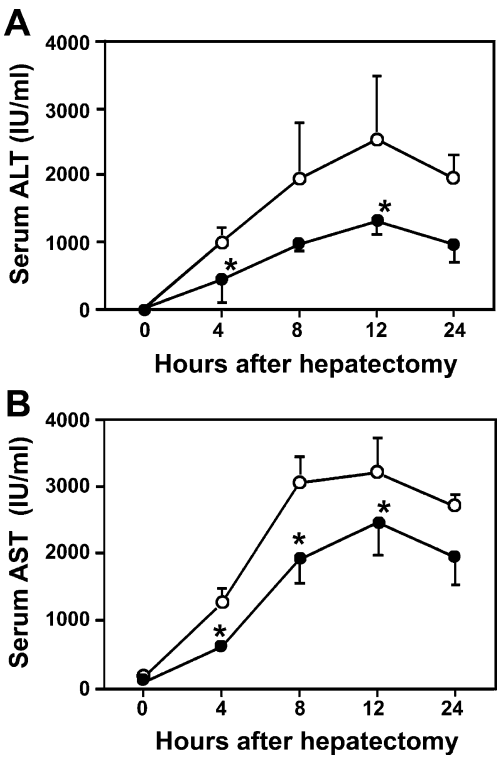


Figure 1 Effects of GGA on serum ALT and AST levels after 90% hepatectomy. Rats pretreated with 100 mg/kg GGA ($n=18$) or vehicle ($n=18$) were subjected to 90% hepatectomy. Serum ALT (**a**) and AST (**b**) levels were measured immediately before (0) or at 4, 8, 12, and 24 h after hepatectomy. Values are means ± SD, $n=8$. *Asterisk*, Significantly different vs. vehicle-treated rats at the respective time points ($P<0.05$ by ANOVA and Scheffé's test).

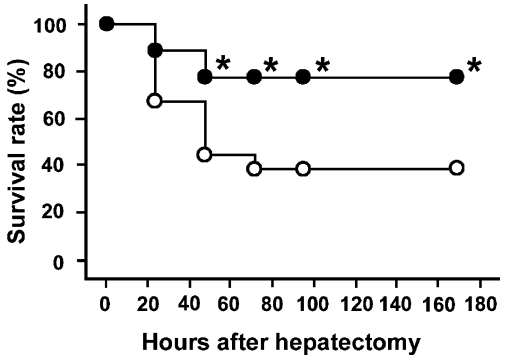


Figure 2 Effect of GGA on survival after 90% hepatectomy. Rats pretreated with 100 mg/kg GGA (n=18) or vehicle (n=18) were subjected to 90% hepatectomy, and their survival were followed until 180 h after hepatectomy.

the operation. Consequently, GGA pretreatment significantly improved survival rate, compared with vehicle pretreatment (Fig. 2). On day 7, 80% of GGA-pretreated rats survived.

Gene Expression Profiles After 90% Hepatectomy

RNA samples were prepared from the remnant livers of vehicle-pretreated rats at 4, 8, 12, and 24 h after 90% hepatectomy; changes in gene expression were measured by microarray using an RNA sample obtained from vehicle-pretreated rats before the operation as a reference control. A total of 640 genes with fluorescence values higher than 500 for both Cy5 and Cy3 signals were selected. We found that 90% hepatectomy changed the mRNA levels of 169 genes by greater than twofold, at least one time point, compared

Table 1 List of Up- or Downregulated Genes After 90% Hepatectomy

Category	Gene symbol (fold change)
Up- or downregulated gene 4 h after 90% hepatectomy	
Cytokine	Gro1 (11.4), IL1R1 (4.77), COL3A1 (2.80)
Stress	GADD45A (5.68), MAPK14 (3.94), PLRG1 (3.39), MDG1 (2.41), HSJ2 (0.37)
Metabolism	CTE1(3.99), GPG3(3.15), POR(2.51), COMT(2.24),FNTA(0.36), FDFT1(0.35)
Others	MYC (7.05), STAT3 (6.16), CYP2C22 (4.19), PIK3R1 (4.11), CCNG1 (4.00), RN.12962 (3.97), PGY1 (0.35), ACATN (0.34), GILZ (0.23), AHR (0.19)
Up- or downregulated gene 8 h after 90% hepatectomy	
Cytokine	IFRD1 (3.82), IL1RN (2.68), IGIFBP (2.14),
Stress	RN48843 (2.96), HSPA5 (2.42), HSPE1 (2.04)
Metabolism	FNTA (3.28), ATP1B1 (3.24), RN.37873 (2.90), BCKDHB (2.87), FDFT1 (2.84), RN.22321 (2.64), GAPD (2.44), RN.19207 (2.06), LDHA (2.02), DHCR7 (2.01), RN.35994 (0.48), ALDH1A1 (0.48), ALDH1A4 (0.47), GSTT2 (0.47), ALDH9A1 (0.45), RN.41757 (0.42), HSD17B2 (0.36)
Signal	ITGB1 (3.22), LOC64194 (3.02), ARF (2.71), MAX (2.16), SAAS (0.46), TEC (0.35)
Receptor	LAMR1 (2.41), RN.55487 (2.39), GHR (0.50), RCSK3 (0.37), NRLH3 (0.49), LOC60351 (0.33)
Transporter	RN.14350 (3.66), SLC16A1 (2.15), NRITP (0.49), RN.44538 (0.36), SLC28A2 (0.35)
TF	NR4A1 (2.26), ATF4 (2.13), STAT1 (0.49), HES1 (0.48)
Cell cycle	CCNG1 (5.25), CCND3 (3.67), RN.15195 (2.02)
Others	KRAS2 (3.39), RB1 (0.32), CYP3A9 (3.82), CYP2D5 (0.38), TIEG (2.41), BCL2L (4.01), CASP6 (0.31)
Up- or downregulated gene 12 h after 90% hepatectomy	
Cytokine	IL18 (2.82), TNFR1 (2.42)
Stress	GADD45A (0.47), HSP27 (0.33), CCS (0.24),
Metabolism	ENO1 (4.08), RN.14535 (2.60), RN.10205 (2.15), COX7A3 (2.06), BCKDHA (0.49), RN.17172 (0.48), DPYD (0.47), MMSDH (0.40), SORD (0.40), RN.22471 (0.40), RN.10622 (0.38), MGMT (0.36), RN.10021 (0.34), HAO3 (0.32), RN.36635 (0.32), RN.67071 (0.31), ADH1 (0.31), LOC64305 (0.30), STE (0.29), BAAT (0.28), EPHX2 (0.20), IDH1 (0.16),
Receptor	P2RY2 (0.40), CD36L1 (0.36), GCGR (0.30), DBI (0.13)
P450	CYP4F4 (0.42), CYP2A1 (0.34), CYP8B1 (0.28), CYP2A2 (0.26), CYP17 (0.17)
Others	JUN (0.41), TCF1 (2.13), KRML (0.20), RN.31120 (0.18), SLC21A7 (0.37), RN.16393 (0.16), TGFB1I4 (0.36), IGFBP1 (0.08) BEX3 (0.25), RN.29790 (0.42)
Up- or downregulated gene 24 h after 90% hepatectomy	
Cytokine	SCYA3 (4.08), IL1b (2.78)
Stress	RN.32702 (7.60), CRPD (2.82), LOC57300 (0.39)
Metabolism	RABGGTB (3.56), RN.46952 (3.49), OGT (2.21), RN.11077 (2.19), HSD11b1 (2.19), RN.6686 (2.08), HADH2 (0.50), SPIN2B (0.49), ES2 (0.45), LCAT (0.42), GAMT (0.41), EPHX1 (0.41), AOX1 (0.39), GSTA2 (0.31), CES1 (0.28), BHMT(0.27), RN.2854 (0.25)
P450	CYP51 (6.39), CYP1A2 (0.44), CYP2J3P1 (0.43), CYP2C23 (0.42), CYP3A3 (0.22), CYP2J4 (0.20)
Cell cycle	PCNA (4.34), RN.65187 (2.63), UBC (0.48)
Receptor	PEX11A (0.50), CD36 (0.42), RN.32282 (0.17)
Others	RPL14 (3.01), C4BPA (3.53), RBBP7 (2.05), SLC21A10 (0.26), HASPP28 (2.61), RN.6236 (5.73), TCEB2 (2.15)

TF Transcription factor

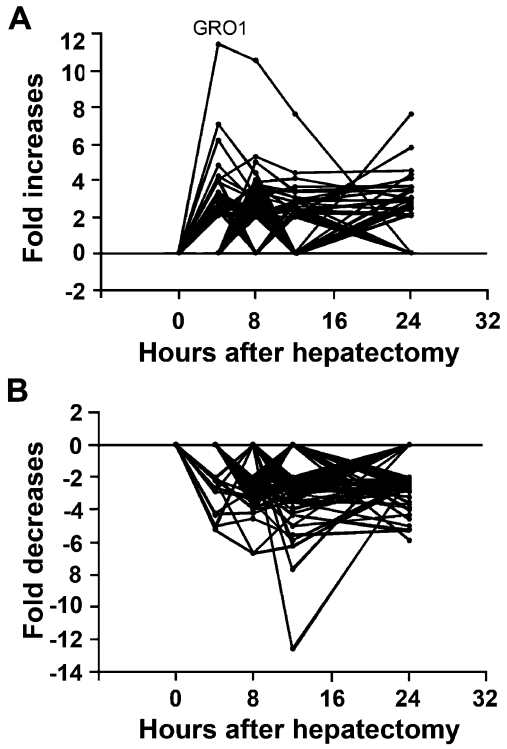


Figure 3 Time-dependent changes in the expression levels of genes significantly responsive to 90% hepatectomy. Among the 1,069 genes examined, 90% hepatectomy induced the upregulation of 74 genes (**a**) and the downregulation of 95 genes (**b**), by greater than twofold, at one time point at least. The operation most remarkably changed the GRO1 mRNA level.

with vehicle-pretreated rats before the operation. These included 74 significantly upregulated genes and 95 downregulated genes, which were categorized and are listed in Table 1. Time-dependent changes in these mRNA levels are shown in Fig. 3. One of the striking features was that ten genes encoding cytokines or cytokine-related molecules were upregulated, while no cytokine-related gene was downregulated (Table 1). Among the upregulated cytokine genes, *GRO1*, encoding a potent chemoattractant belonging to the CXC chemokine subfamily, was most rapidly and markedly upregulated after 90% hepatectomy (Fig. 3a). Among HSP genes, two genes (*HSPA5* and *HSPE1*) were upregulated, while three genes (*HSJ2*, *CCS*, and *HSP27*) were downregulated.

We also examined how GGA pretreatment modified the changes in gene expression after 90% hepatectomy. For this purpose, gene expression was compared between GGA- and vehicle-pretreated rats before surgery and 4, 8, 12, and 24 h after the surgery. GGA pretreatment upregulated nine genes (*ADH1*, *ADH4*, *PRLR*, *POR*, *EPHX1*, *RN.10854*, *HSPA5*, *HSP70*, and *MYC*) and downregulated 11 genes (*RN.16393*, *IFRD1*, *IL1R1*, *SCYA5*, *IGFBP1*, *BCKDK*, *ATP1B1*, *HAO3*, *IL18*, *RN.37873*, and *LOC64194*) by greater than twofold prior to the operation. GGA changed the levels of small numbers of mRNAs by greater than twofold at 4 and 8 h after the operation, compared with vehicle pretreatment: GGA upregulated the expression of seven (*MX1*, *IGFBP1*, *FDFT1*, *RN.16393*, *HSPA5*, *HSP70*, and *HSP27*) and nine genes (*CYP2D5*, *RN.31120*, *ADH1*, *SORD*, *RN.10021*, *HSPA5*, *HSP70*, *HSP27*, and *SLC30A2*) at 4 and 8 h after the operation, respectively, and downregulated five (*GRO1*, *HSD17B2*, *CYP8B1*, *TIEG*, and *AML1*) and three (*GRO1*, *ATP1B1*, and *RN.30070*) genes at the same time points. However, at 12 and 24 h after the operation, GGA up- or downregulated the expression levels of larger numbers of genes (Table 2).

Validation of Microarray Data

Consistent with microarray data (Table 2), both RT-PCR (Fig. 4a) and Northern hybridization (Fig. 4b) showed that

Table 2 List of Up- or Downregulated Genes with GGA

Category	Gene symbol (fold change)
Up- or downregulated genes with GGA 12 hours after 90% hepatectomy	
Cytokine	SCYA2 (3.67), IL1b (3.44), IL1a (3.05), IL1RN (2.46), SCYA3 (2.30), CEBPB (2.27), GRO1 (0.31)
Stress	HSP27 (3.64), HSPA5 (2.48), CPT2 (0.47)
Metabolism	ADH1 (2.48), FDFT1 (2.36), BHMT (0.32), HSD17B2 (0.36), STE (0.39), BAAT (0.45)
Signal	RN.31120 (4.75), JAK2 (2.78), LOC64194 (2.69), ICAM1 (2.66)
Apoptosis	TNFIP6 (4.58), BIRC2 (3.32), TDAG (2.08)
Others	HES1 (0.43), PCYP51 (3.10), CYP8B1 (0.35), RN.12962 (4.75), RN.16393 (10.72), IGFBP1 (15.91), EGFR (2.03), ADORA2B (0.26), AHR (0.43)
Up- or downregulated genes with GGA 24 h after 90% hepatectomy	
Cytokine	SCYA2 (3.84), SCYA3 (2.45), Gro1 (0.36)
Stress	HSP27 (2.30), HSPA5 (2.10), RN.32702 (0.33)
Metabolism	AFAR (4.11), COMT (2.66), EPHX1 (2.53), RN.34327 (2.29), HMGCR (2.28), BCKDHB (2.27), GAMT (2.24), ALDH1A1 (2.16), ADH1 (2.08), BCKDK (2.03)
Transporter	CMOAT (2.06), RN.16393 (0.38), SLC18A2 (0.40)
Others	CYP3A3 (3.06), CYP4B2 (0.32), WNT4 (0.32), PAK1 (2.06), IGFBP1 (0.25), ADORA2B (3.14), GCGR (2.08)

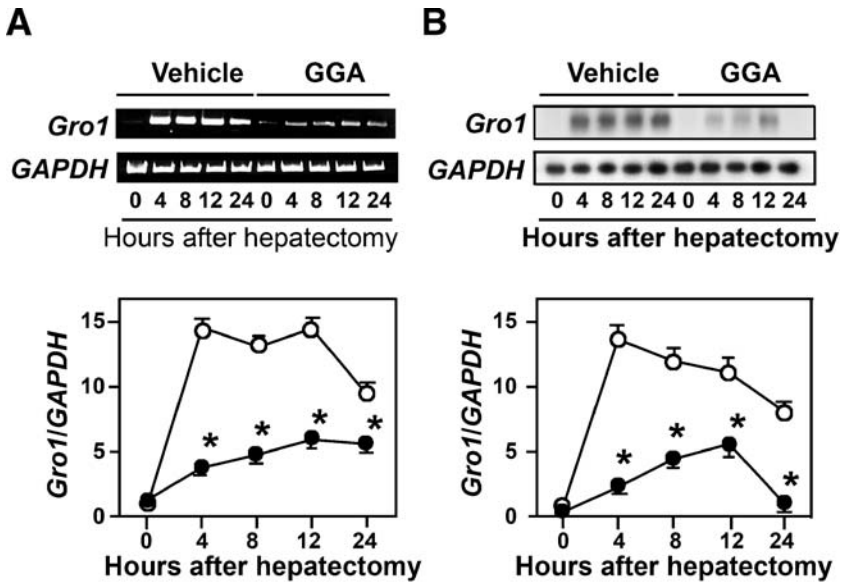
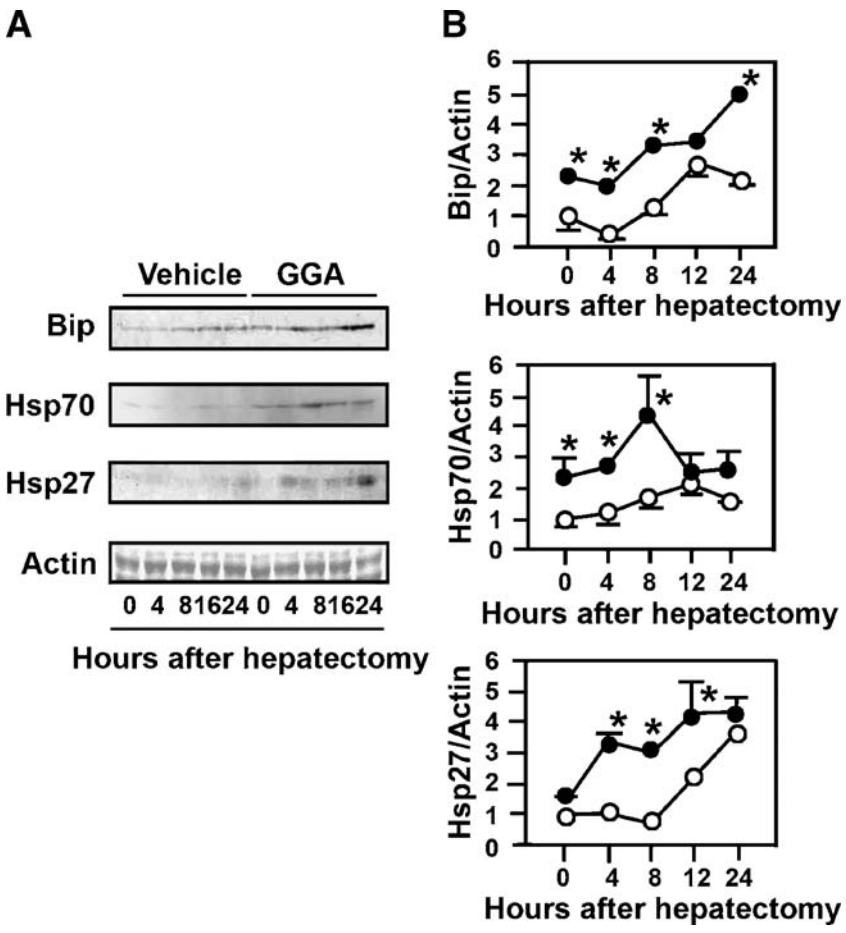


Figure 4 Effect of 90% hepatectomy on GRO1 mRNA expression and its modification with GGA. After pretreatment with 100 mg/kg GGA (n=5) or vehicle (n=5), rats were subjected to 90% hepatectomy. Total RNA was prepared immediately before (0) or 4, 8, 12, and 24 h after the surgery. The amounts of GRO1 mRNA were measured by RT-PCR (**a**) or Northern hybridization (**b**) using GAPDH mRNA as an internal control and were quantified by densitometric analysis. Values are means ± SD, n=5. *Asterisk*, significantly different vs. vehicle-treated rats at the respective time points (P<0.05 by ANOVA and Scheffé's test).

Figure 5 Effect of GGA on HSP induction after 90% hepatectomy. **a** Rats pretreated with 100 mg/kg GGA (n=5) or vehicle (n=5) were subjected to 90% hepatectomy. Protein was extracted immediately before (0) or 4, 8, 12, and 24 h after the surgery, and the amounts of BIP, HSP70, and HSP27 were measured by immunoblot analysis as described in the "Material and methods." **b** The amounts of each HSP were quantified by densitometric analysis using β-actin as an internal standard. Values are means ± SD, n=5. *Asterisk*, significantly different vs. vehicle-treated rats at the respective time points (P<0.05 by ANOVA and Scheffé's test).



pretreatment with GGA significantly suppressed *GRO1* mRNA expression after 90% hepatectomy.

We also confirmed that GGA pretreatment significantly increased the levels of BIP and HSP70 before the operation (Fig. 5). Furthermore, the levels of BIP, HSP70, and HSP27 were significantly increased in the remnant liver tissues of GGA-pretreated rats at the indicated time points during the 24 h after the surgery, compared with those of vehicle-pretreated rats (Fig. 5).

Discussion

In the present study, we examined changes in gene expression in the remnant liver during the 24 h after 90% hepatectomy and found that *GRO1* was most rapidly and remarkably upregulated after the hepatectomy. *GRO1* encodes a member of the CXC chemokine subfamily that is the murine counterpart of human growth-related oncogene α. GRO1 is a potent chemoattractant for granulocytes and provokes inflammation.[18–22] It is possible that GRO1 plays a crucial role in acute liver injury after massive hepatectomy. In addition to *GRO1*, nine genes encoding cytokines or cytokine-related molecules (*IL1R1*, *COL3A1*, *IFRD1*, *IL1RN*, *IGIFBP*, *IL18*, *TNFR1*, *SCYA3*, and *IL1β*) were also upregulated during the 24 h after 90% hepatectomy, while GGA pretreatment selectively suppressed the upregulation of *GRO1* mRNA expression. These results suggest that GGA may exert protective actions through suppressing inflammation and that GRO1 may be one of the potential targets for GGA. In glomerular mesangial cells, GGA was reported to block activation of nuclear factor-κB and consequent induction of monocyte chemoattractant protein 1 by inflammatory cytokines.[23] At present, it is unclear whether GGA directly affects these inflammatory mediators, or it indirectly suppresses inflammatory responses through induction of HSP70.

Using HSF1-deficient mice, it has recently shown that GGA HSF1 dependently exerts its protective actions.[24] We reconfirmed again that GGA enhanced HSP70 induction in our experimental model. HSP70 exerts protective actions under stressful conditions through its chaperone functions,[11] direct interferences with cell death pathways including apoptosis and necrosis,[25,26] and suppression of inflammation.[27–29] The mechanisms of anti-inflammatory regulation by HSP70 are mostly uncharacterized. However, a recent study has shown that HSP70 not only inhibits high-mobility group box 1 (HMGB1), a nuclear protein that has recently been identified as an important mediator of local and systemic inflammatory diseases when released into the extracellular milieu, but also suppresses the proinflammatory activities of HMGB1.[30] Further studies are needed to elucidate the mechanism for the inhibition of *GRO1* expression with GGA.

GGA also enhanced the induction of HSP27, a constitutively expressed cytoplasmic protein, and translocates into the nucleus in response to stress. HSP27 acts as a regulator of the intracellular redox state and is a potent inhibitor of apoptosis.[31] The upregulation of HSP27 in response to GGA may, at least in part, participate in the GGA-induced protection against liver injury after massive hepatectomy.

It should be also noted that GGA upregulated constitutive and hepatectomy-induced expression of BIP. BIP is an endoplasmic reticulum (ER) member of the Hsp70 family and plays an essential role in protein folding and quality control in the ER.[32] It also serves as a sensor for ER stress.[33] Hemodynamic and metabolic overloading on the small remnant, functional liver is a primary cause of acute hepatic failure after massive hepatectomy. In a previous study, we reported the appearance of abnormally enlarged ER-like, eosinophhilic, and hyaloid bodies after 95% hepatectomy. We could not detect similar structures in the case of 90% hepatectomy; however, it is reasonable to consider that ER stress and the unfolded protein response (UPR) may be involved in the overload-induced damage. Hayakawa et al. also reported that GGA stimulated expression of BIP and suppressed ER stress in glomerular mesangial cells.[23] Thus, GGA may also exert its protective action through stimulation of the UPR response.[23] Elucidation of this molecular mechanism is currently underway.

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Multiagent Chemotherapy for Isolated Colorectal Liver Metastases: A Single-centered Retrospective Study

Srinevas K. Reddy · Gloria Broadwater · Donna Niedzwiecki · Andrew S. Barbas · Herbert I. Hurwitz · Johanna C. Bendell · Michael A. Morse · Bryan M. Clary

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Abstract
Background Few studies identifying variables associated with prognosis after resection of colorectal liver metastases (CLM) account for treatment with multiagent chemotherapy (fluoropyrmidines with irinotecan, oxaliplatin, bevacizumab, and/or cetuximab). The objective of this retrospective study was to determine the effect of multiagent chemotherapy on long-term survival after resection of CLM.
Methods Demographics, clinicopathologic tumor characteristics, treatments, and long-term outcomes were reviewed.
Results From 1996 to 2006, 230 patients underwent resection of CLM. Treatment strategies before and after resection included fluoropyrimidine monotherapy (n=34 and n=39), multiagent chemotherapy (n=81 and n=73), and observation (n=115 and n=118). Prehepatectomy treatment strategy was not associated with overall survival. Actuarial 4-year survival was 63%, 39%, and 40% for patients treated with multiagent chemotherapy, fluoropyrimidine monotherapy, and observation after hepatectomy, p=0.06. Posthepatectomy multiagent chemotherapy (p=0.04, HR 0.52 [0.27–1.03]), duration of posthepatectomy chemotherapy treatment of 2 months or longer (p=0.05, HR 0.49 [0.25–0.99]), carcino-embryonic antigen level >10 ng/mL (p=0.03, HR 2.09, 95% CI [1.32–3.32]), and node positive primary tumor (p=0.002, HR 1.79 [1.06–3.02]) were associated with overall survival in multivariate analysis.
Conclusions The association of posthepatectomy multiagent chemotherapy with overall survival in this retrospective study indicates the need for prospective randomized trials comparing multiagent chemotherapy and fluoropyrimidine monotherapy for CLM.

Keywords Colorectal liver metastases · Chemotherapy · Hepatic resection

S. K. Reddy (✉) · A. S. Barbas · B. M. Clary
Department of Surgery, Duke University Medical Center,
Box 3247, Durham, NC 27710, USA
e-mail: reddy005@mc.duke.edu

G. Broadwater
Department of Cancer Center Biostatistics,
Duke University Medical Center,
Durham, NC 27710, USA

D. Niedzwiecki
Department of Biostatistics and Bioinformatics,
Duke University Medical Center,
Durham, NC 27710, USA

H. I. Hurwitz · J. C. Bendell · M. A. Morse
Department of Medicine, Duke University Medical Center,
Durham, NC 27710, USA

Introduction

Classical prognostic factors pertaining to survival after resection of colorectal liver metastases (CLM) are derived from large, retrospective resection series.[1–41] Multiagent systemic chemotherapy regimens, comprising combinations of fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab, and/or cetuximab, have improved the prognosis for patients with stage III and unresectable stage IV colorectal cancer compared to fluoropyrimidine monotherapy.[42–44] Based on these survival benefits, multiagent chemotherapy regimens are frequently utilized in the treatment of patients with resectable CLM.[45] Recently, reported results from the EORTC 40983 phase III study, which noted an improvement in progression-free survival after treatment with perioperative FOLFOX4 compared to observation for initially resectable CLM,[47] will further increase the use of this and other multiagent chemotherapy regimens for this patient popula-

tion. However, none of the large retrospective studies evaluating demographic, clinicopathologic, and treatment variables associated with survival after resection of CLM account for multiagent chemotherapy treatment despite their widespread use. Thus, the objective of this retrospective study was to (1) determine whether multiagent chemotherapy was associated with long-term survival after resection of CLM in a single-center treatment experience and (2) identify factors associated with overall survival after partial hepatectomy among a cohort of patients in which a substantial portion were treated with multiagent chemotherapy.

Methods

CLMs were diagnosed with computed tomography or magnetic resonance imaging; positron emission tomography was used to confirm positive findings in more recent patients. Extrahepatic metastatic disease was also identified using these imaging modalities. Patients with unresectable extrahepatic metastatic disease were typically not offered resection. Following laparotomy and exploration for extrahepatic metastatic disease, coronary and falciform ligaments were divided as necessary to achieve adequate liver mobilization for larger resections. Intraoperative ultrasound was utilized to confirm the presence of CLM identified on preoperative imaging, ascertain the presence of CLM undetected by preoperative imaging, assess lesion proximity to major vessels, and outline transection planes. For cases in which CLM were not apparent on intraoperative visual inspection or ultrasound examination, hepatic resection was performed based upon lesion dimensions and proximity to major vascular and/or biliary structures as identified on preoperative imaging. Thus, resections were performed for both gross and microscopic disease. Inflow control (either total or selective), extrahepatic hepatic venous outflow control, and inflow occlusion were performed at the discretion of the operating surgeon. Selective inflow control was defined as individual intrahepatic ligation of a segmental pedicle prior to parenchymal transection. Total inflow occlusion was accomplished with the Pringle maneuver. Small perforating branches from the right hemiliver to the inferior vena cava were divided for right hemiliver resections. Extrahepatic vein and/or portal pedicle division was commonly performed with a reticulated 60×2.5-mm vascular stapler. For large-volume resections, central venous pressure was kept below 5 mm Hg with the use of early intraoperative fluid restriction and vasoactive agents. Hepatic transection was performed with a variety of techniques including crush-clamping, vascular staplers, the Harmonic Scalpel (UltraCision, Ethicon Endosurgery, Somerville, NJ, USA), and the Tissue Link® device (TissueLink Medical, Dover, NH, USA). Crush-clamping and vascular staplers were most commonly used. For crush-clamp transection, the liver parenchyma was crushed with Kelly clamps in serial fashion. Small vessels and biliary structures were coagulated with electrocautery; larger (>2 mm) vessels and biliary radicals were ligated or clipped. After 2001, argon beam coagulation was commonly applied to the transection edge to stop residual bleeding.

There were no uniform criteria for the administration of chemotherapy before or after partial hepatectomy. The specific drug combination used for each patient was at the discretion of the treating medical oncologist. Thus, no particular regimen was selected as first-line therapy. Fluoropyrimidine monotherapy [modalities of treatment included intravenous, oral, or via hepatic arterial infusion (HAI)] with or without leucovorin was used before 2000. As HAI consisted of floxuridine, no distinctions were made between systemic and regional fluoropyrimidine therapy in this study. Thus, a regimen consisting of HAI or HAI with 5-FU was categorized as fluoropyrimidine monotherapy, whereas a regimen including HAI with oxaliplatin, irinotecan, bevacizumab, and/or cetuximab was categorized as multiagent chemotherapy. From 2000–2006, multiagent chemotherapy (e.g., combinations of fluoropyrmidines, irinotecan, oxaliplatin, bevacizumab, and/or cetuximab) was preferentially utilized, when tolerated.

After obtaining Institutional Review Board approval, demographics, clinicopathologic tumor characteristics, medical and surgical treatments, and long-term outcomes from patients identified from a hepatectomy database who underwent hepatic resection for CLM were reviewed. Resections were categorized as nonanatomic if one or more CLMs were extirpated with a wedge resection. Prehepatectomy chemotherapy included treatment after discovery of metastatic disease and before hepatic resection. Downsizing of CLM indicated conversion of unresectable to resectable disease after treatment with prehepatectomy chemotherapy. Patients with synchronous CLM who were treated exclusively with a short course of fluoropyrimidine chemotherapy with the purpose of enhancing the effectiveness of neoadjuvant radiotherapy for rectal cancer were categorized as not having received prehepatectomy chemotherapy. Posthepatectomy chemotherapy included treatment after hepatic resection and before disease relapse. Duration of chemotherapy treatment was calculated from the initial to the final dose of therapy. Hepatic resections were described according to standard nomenclature.[48] Major hepatectomy was defined as resection of at least three segments. To focus on individuals with isolated hepatic metastases who underwent extirpation with curative intent and were eligible for long-term follow-up, patients with extrahepatic metastatic disease at hepatectomy, with grossly positive hepatic resection margins (R_2 resection), or who suffered posthepatectomy mortality were excluded from analysis.

Statistical comparisons were carried out with SAS software (SAS Institute, Cary, NC, USA). For the purposes of this study, prehepatectomy and posthepatectomy chemotherapy were categorized as separate variables. That is, treatment with multiagent or fluoropyrimidine prehepatectomy chemotherapy was independent from multiagent or fluoropyrimidine posthepatectomy treatment. The Wilcoxon rank sums test was used to compare demographics, treatments, and clinicopathologic tumor characteristics (1) between patients who received multiagent chemotherapy vs. fluoropyrimidine-based monotherapy vs. observation before hepatic resection, and (2) between patients who received multiagent chemotherapy vs. fluoropyrimidine based monotherapy vs. observation after hepatic resection. Overall and recurrence-free survival after hepatic resection were estimated by the Kaplan–Meier method. Overall survival was measured from date of resection until death from any cause. Recurrence-free survival was measured from date of resection until documented disease recurrence or death from any cause. Patients who were alive or without disease recurrence at last follow-up were censored at the date of last follow-up. Covariates were modeled using both univariate and multivariate Cox proportional hazards regression to predict disease-free and overall survival. Dummy variables were used to describe categorical variables with three levels and were tested jointly. Multivariate Cox proportional hazards models were constructed using the backward selection technique with an alpha of 0.20 for both the alpha level to stay and the alpha level to enter the model. Sample sizes in each analysis varied according to the variables entered. Again, the variable of prehepatectomy chemotherapy treatment (none, fluoropyrimidine based monotherapy, of multiagent chemotherapy) was considered independent from the variable of posthepatectomy chemotherapy treatment (none, fluoropyrimidine based monotherapy, of multiagent chemotherapy) for the survival analyses. A significance level of 0.05 was used for these analyses.

Results

Demographics and Treatments

From 1996 to 2006, 289 consecutive patients underwent resection of CLM. After exclusion of patients with extrahepatic metastatic disease (n=37), with gross disease after hepatectomy (n=32), and who suffered posthepatectomy mortality (n=10), 230 patients were analyzed in this study. No primary T stage, primary N stage, or prehepatectomy carcino-embryonic antigen (CEA) data were available for 37, 17, and 17 patients, respectively. Two patients received fluoropyrimidine monotherapy via HAI before hepatic resection. Multiagent prehepatectomy chemotherapy regimens included oxaliplatin based therapy with (n=22) and without (n=13) bevacizumab; irinotecan-based regimens with bevacizumab (n=1), with cetuximab (n=2), or without antibiologic agents (n=33); and 5-fluorouracil (5-FU) with bevacizumab (n=5). Five patients received sequential oxaliplatin followed by irinotecan-based therapy because of chemotoxicity. Twenty-one patients who received fluoropyrimidine monotherapy and six patients treated with fluoropyrimidines and irinotecan after hepatic resection received HAI. Other multiagent posthepatectomy regimens included 5-FU with bevacizumab (n=9); irinotecan-based therapy with bevacizumab (n=4), with cetuximab (n=2), or without antibiologic agents (n=17); oxaliplatin-based therapy with (n=18) and without bevacizumab (n=14); and bevacizumab alone (n=1). Two patients received sequential oxaliplatin followed by irinotecan-based therapy because of chemotoxicity. Eighteen percent of patients were treated with similar chemotherapy regimens before and after hepatic resection (4.8% fluoropyrimidine monotherapy and 14% multiagent chemotherapy).

There were differences in several demographic, clinicopathologic, and treatment variables between patients treated with multiagent chemotherapy, fluoropyrimidine monotherapy, or observation before and after hepatic resection (Table 1). For prehepatectomy treatment, these included disease-free interval (DFI) from resection of primary tumor to discovery of CLM, CEA, size of largest CLM, number of CLM, and year of hepatic resection. Patients with four or more CLM were more frequently treated with multiagent chemotherapy before hepatic resection compared to fluoropyrimidine monotherapy or observation. For posthepatectomy chemotherapy treatment, significant differences were observed in patient age, CEA, and year of surgery.

Long-term Outcomes

Median follow-up after hepatic resection for all patients was 40 months. Patients treated with posthepatectomy multiagent chemotherapy, fluoropyrimidine monotherapy, and observation had median follow-up of 26, 41, and 74 months after hepatic resection, respectively. Due to the short follow-up in patients treated with multiagent chemotherapy, we estimated 2- and 4-year survival in each subgroup.

Median recurrence-free survival after hepatic resection for all patients was 17 months. One hundred twenty (52%) patients had disease recurrence at last follow-up. The sites of disease recurrence were extrahepatic, intrahepatic, and both extra- and intrahepatic in 49%, 33%, and 18% of these patients. Synchronous presentation of CLM with primary colorectal cancer (DFI=0), four or more CLM, and T_3/T_4 cancers were associated with shorter recurrence-free sur-

Table 1 Demographics, Clinicopathologic Tumor Characteristics, and Surgical Treatments for Patients who Underwent Resection of Colorectal Liver Metastases

Variable	All (%)		Prehepatectomy chemotherapy							Posthepatectomy chemotherapy						
	(*n*=230)		Observation (*n*=115)		Fluoro (*n*=34)		Multiagent (*n*=81)		*p*	Observation (*n*=118)		Fluoro (*n*=39)		Multiagent (*n*=73)		*p*
	n	%	*n*	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Median age (years)	61		62		57		59		0.11	66		57		55		0.001
	33–83		33–83		37–79		34–77			33–82		34–78		34–83		
Age ≥65 years	88	38	46	40	11	32	31	38	0.72	62	53	12	31	14	19	0.001
Male	137	60	70	61	18	53	49	60	0.76	68	58	23	59	46	63	0.76
Rectal primary	52	23	26	23	15	44	11	14	0.42	24	21	12	31	16	22	0.42
T_3/T_4 primary	167	87	82	86	23	88	62	86	0.59	82	89	30	83	55	85	0.59
Node pos. 1°	144	68	67	63	23	77	54	71	0.77	75	69	24	63	45	67	0.77
1° adj. therapy	87	38	61	53	10	29	16	20	0.40	48	41	16	41	23	32	0.40
DFI (months)																
DFI=0	106	54	22	19	24	71	60	74	0.001	47	41	17	44	42	56	0.13
Median[a]	16		16		15		17		0.62	16		16		14.5		0.61
	1–136		2–136		2–60		1–45			1–136		2–73		1–66		
CEA (ng/mL)	8.1		10.7		8.4		5.6		0.01	9.1		11.2		7.0		0.03
	0.6–3244		0.6–3244		0.6–580		0.7–939			0.6–3244		0.6–580		0.7–1042		
≥ 10 ng/mL	96	45	58	53	13	41	25	36	0.05	51	46	21	60	24	36	0.06
Median size (cm)	3.5		3.5		3.5		3.1		0.05	3.5		3.9		3.2		0.12
	0–25		0.7–25		1.1–12.0		0–120			0–14.7		1.5–25		0–20		
Size >5 cm	71	31	46	36	8	30	17	26	0.34	39	31	14	42	18	27	0.25
Median no. CLM	1		1		1		2		0.03	1		1		1		0.11
	1–10		1–10		1–4		1–10			1–10		1–10		1–10		
≥4 lesions	27	12	10	9	1	3	16	21	0.01	11	9	8	21	8	11	0.15
Downsize	13	6	—	—	3	9	10	12	—	5	4	3	8	5	7	0.43
Nonanatomic	88	38	37	40	10	29	35	43	0.04	40	34	15	38	33	45	0.59
Major resection	144	63	65	58	20	62	59	73	0.11	76	65	26	69	42	59	0.51
R_1 resection	13	6	8	7	1	3	4	5	0.68	6	5	5	13	2	3	0.09
DOS 2001–2006	164	71	82	71	11	32	71	88	0.001	72	61	21	54	71	92	0.001

Nonanatomic refers to any portion of partial hepatectomy that included a nonanatomic resection. Downsize refers to conversion of unresectable liver disease to resectable disease due to reduction in size and/or number of CLM after prehepatectomy chemotherapy. All continuous variables listed as median (range). Percentages for categorical variables are calculated based on patients with available data.

Fluoro fluoropyrimidine monotherapy, *1° adj*. chemotherapy given after primary tumor resection and before discovery of CLM, *DFI* disease-free interval from resection of primary tumor to discovery of liver metastases, *CEA* carcinoembryonic antigen, *CLM* colorectal liver metastases, *Size* size of largest CLM, *R_1 resection* microscopic positive hepatic resection margins, *DOS* date of surgery from years 2001 to 2006, *Major resection* resection of three or more segments

[a] Median DFI for patients with metachronous metastases.

vival on multivariate analysis (Table 2). Neither prehepatectomy nor posthepatectomy treatment strategy was associated with recurrence-free survival.

Two-year actuarial, 4-year actuarial, and median overall survival after hepatic resection for all patients were 75%, 45%, and 42 months. Node positive primary disease, CEA >10 ng/mL, posthepatectomy treatment with multiagent chemotherapy, and duration of posthepatectomy chemotherapy treatment for 2 months or longer were associated with overall survival in multivariate analysis (Table 2). Median, 2-year, and 4-year actuarial overall survival for patients treated with posthepatectomy multiagent chemotherapy, 5-FU monotherapy, and observation were: not attained, 84% and 63%; 34 months, 69% and 39%; and 35 months, 72% and 40%; $p=0.06$ (Fig. 1). Prehepatectomy treatment strategy was not associated with overall survival. Median, 2-year, and 4-year actuarial overall survival for patients treated with prehepatectomy multiagent chemotherapy, 5-FU monotherapy, and observation were 43 months, 82% and 49%; 34 months, 74% and 46%; and 39 months, 71% and 42%; $p=0.06$.

Among patients who were treated with posthepatectomy fluoropyrimidine-based chemotherapy, there were no significant differences in long-term outcomes between patients treated with and without HAI therapy. Median recurrence-free survivals of the 21 patients treated with HAI and the 18

Table 2 Univariate and Multivariate Analysis of Variables Associated with Disease Free and Overall Survival

Variable	Recurrence-free survival			Overall survival		
	Univariate *p*	Multivariate *p*	MVA HR (95% CI)	Univariate *p*	Multivariate *p*	MVA HR (95% CI)
Age ≥65 years	0.71	–	–	0.13	–	–
Male	0.47	–	–	0.54	–	–
Rectal primary cancer	0.33	–	–	0.56	–	–
T_3/T_4 primary cancer	0.16	0.070	1.83 (0.95–3.52)	0.42	–	–
Node positive primary	0.041	–	–	0.009	0.03	1.79 (1.06–3.02)
Primary adj. therapy	0.42	–	–	0.44	–	–
DFI (months)	0.011	0.003				
1–12 vs. 0			1.20 (0.76–1.91)	0.27	–	–
≥12 vs. 0			0.51 (0.31–0.83)			
CEA ≥10 ng/mL	0.13	–	–	0.001	0.002	2.09 (1.32–3.32)
Size >5 cm	0.91	–	–	0.39	–	–
≥4 CRM	0.006	0.02	1.89 (1.11–3.20)	0.31	–	–
Downsize	0.11	–	–	0.16	–	–
Nonanatomic resection	0.20	–	–	0.27	–	–
Major resection	0.85	–	–	0.15	–	–
Hepatic margins	0.82	–	–	0.36	–	–
Positive vs. <1 cm						
<1 cm vs. ≥1 cm						
Positive vs. ≥1 cm						
DOS ≥2001	0.22	–	–	0.07	–	–
Preop chemo	0.57	–	–	0.60	–	–
Multiagent vs. none						
Fluoro vs. none						
Multiagent vs. Fluoro						
Postop chemo	0.96	–	–	0.06	0.04	
Multiagent vs. none						1.13 (0.49–2.60)
Fluoro vs. none						2.15 (1.06–4.35)
Multiagent vs. Fluoro						0.52 (0.27–1.03)
Preop chemo ≥2 mo.	0.76	–	–	0.65	–	–
Postop chemo ≥2 mo.	0.83	–	–	0.10	0.05	0.49 (0.25–0.99)

Nonanatomic refers to any component of a hepatic resection that involved a wedge resection of CLM

Chemo chemotherapy, *Fluoro* fluoropyrimidine monotherapy, *MVA* multivariate, *Preop* prehepatectomy, *Postop* posthepatectomy, *CLM* colorectal liver metastases, R_1 microscopic positive hepatic resection margins, *DFI* disease-free interval from resection of primary tumor to discovery of liver metastases, *Primary adj. therapy* chemotherapy given after primary tumor resection and before discovery of CLM, *Major hepatectomy* resection of three or more hepatic segments, *Size* size of largest CLM, *Downsize* conversion of unresectable liver disease to resectable disease due to reduction in size and/or number of CRM after prehepatectomy chemotherapy, *DOS ≥2001* date of surgery from 2001 to 2006, *≥2 mo.* duration of prehepatectomy or posthepatectomy chemotherapy of at least 2 months

patients who were not treated with HAI were 24 and 10 months, respectively (p=0.36). Median, 2-year, and 4-year actuarial overall survival for patients treated with and without HAI were 47 months, 74% and 46%, vs. 29 months, 63% and 26% (p=0.72).

Discussion

Rationale for the acceptance of surgical extirpation and multiagent chemotherapy for resectable CLM are mainly derived from large, retrospective resection series and level I data for other stages of colorectal cancer. Numerous large, retrospective studies over the past 20 years have demonstrated long-term survival after resection of CLM (Table 3). Conclusions from these case series have also established various demographic and clinicopathologic parameters predictive of survival after resection; prognostic scoring systems based on these variables have been created and validated.[10,12,18] Multiagent chemotherapy regimens are widely utilized for patients with isolated CLM because (1) of the proven benefits relative to systemic fluoropyrimidine monotherapy for patients with stage III and unresectable stage IV disease[42] and (2) disseminated microscopic disease frequently persists after resection of CLM as more than 70% of patients in most studies experience disease relapse within 5 years of an R_0 resection.[2,3,5–8,11,12,16,17,19,23,31–33,36,37,39,45] Accordingly, the National Comprehensive Cancer Network

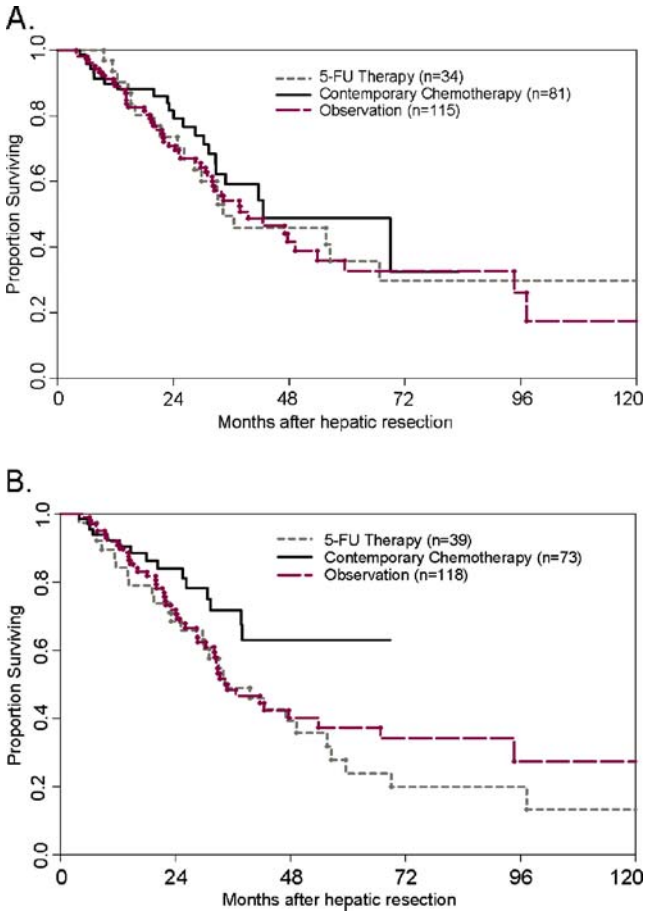

Figure 1 Overall survival after resection of CLM by treatment strategy before (**A**) and after (**B**) hepatic resection. Long-term survival outcomes are summarized for all patients (n=230) in each figure.

recommends treatment with systemic multiagent chemotherapy after resection of CLM for patients that can tolerate intensive therapy.[49] While the EORTC 40983 phase III trial demonstrated a recurrence-free survival benefit for perioperative FOLFOX4 compared to no chemotherapy for patients who ultimately underwent resection of CLM,[47] no study has compared the efficacy of multiagent chemotherapy relative to systemic fluoropyrimidine monotherapy for these patients. To help provide rationale for the creation of large prospective randomized studies that shed light on this important issue, we reviewed our experience in resected patients to determine the effects of multiagent chemotherapy on long-term outcomes after resection of CLM and to determine whether classical factors associated with survival are still relevant in the era of multiagent chemotherapy.

As multiagent posthepatectomy chemotherapy and not lesion size nor number of CLM were associated with overall survival in our study (Table 2 and Fig. 1), multiagent chemotherapy may alter the traditional prognostic landscape for patients with isolated CLM. Retrospective analysis of large hepatic resection series have identified variables associated with long-term survival after extirpation. These include DFI, size and number of CLM, total CLM volume, patient age and gender, extrahepatic metastatic disease, primary or portal lymph nodal involvement, hepatic resection margin status, and prehepatectomy CEA level (Table 3). However, many of these studies do not report the number of patients treated with chemotherapy, are comprised of patients not treated with chemotherapy before or after partial hepatectomy, or do not account for chemotherapy treatment in analyses of overall survival after hepatic resection.[2,3,8,13,16–18,25,30,35] Several reports that did account for chemotherapy in outcomes analyses note that posthepatectomy chemotherapy did not affect overall survival.[1,4,5,9,11,12,14,21,23,26,27,31,39] However, fluoropyrimidine monotherapy was utilized in nearly all patients in these series, limiting the relevance of these studies to the current era. Three studies have shown that posthepatectomy chemotherapy was associated with overall survival; only one of these studies included a substantial proportion of patients treated with multiagent chemotherapy (Table 3).[6] Thus, our study is exceptional in that we not only examined the effects of chemotherapy on long-term outcomes but also treatment duration and, specifically, the use of multiagent regimens. Clinicopathologic liver tumor characteristics classically associated with poor outcome, such as large lesion size, four or more CLM, and synchronous presentation with the primary tumor, were not associated with poor overall survival in our study (Table 2). This corresponds with the altered definition of "resectable" CLM from traditional standards of less than four liver lesions, unilobar disease, and proximity of at least 1 cm to major vessels to new criteria of anticipated complete resection of CLM with sparing of two adjacent liver segments with intact vascular inflow, outflow, and biliary drainage that comprise at least 20% of the prehepatectomy liver volume (in patients with normal underlying liver).[50] Thus, resectabilty has evolved from being defined by what is removed to what will remain after extirpation. Because large lesion size and four or more CLMs were not associated with poor overall survival, the results of our study suggest that multiagent chemotherapy contributes to this de-emphasis on macroscopic hepatic tumor burden. The increased prevalence of posthepatectomy chemotherapy treatment (particularly with multiagent regimens) may explain why a more recent date of hepatic resection has been associated with improved survival in some studies[5,11,21] and why modern resection series report better long-term outcomes as compared to older studies (Table 3). Enhancements in the quality of prehepatectomy radiologic imaging, intraoperative ultrasound, and hepatic transection techniques may also contribute to these superior outcomes.

While the variety of multiagent chemotherapy regimens and treatment durations in our study prevents adequate

Table 3 Factors Associated with Overall Survival from Large Retrospective Series of Hepatic Resection for Colorectal Metastases Listed Chronologically

Author	*n*	Chemo	Median OS	3-year OS	5-year OS	Gender	Age	Primary node	Rectal tumor	Primary T	Primary stage	CEA	DFI	EHD	CLM volume	#	Bilobar	Size	Satellitosis	Portal nodes	Grade	DOS	Blood tx	Anatomic	Margin	Postop chemo
Hughes et al[28,29b]	800[a]	NR			32%			•				•	•	•		•									•	
Doci et al[33]	100	NR	28		30%						•				•											
Ooijen et al[19]	118[a]	NR	26		21%																					
Donato et al[47]	102[a]	39% postop	29	36%		•							•													
Hohenberger et al[36]	141	NR	34			•						•	•		•											
Nordlinger et al[12]	1568[a]	35% postop		44%	28%		•	•		•		•	•			•		•							•	
Jamison et al[26,27]	280	33% postop	32	46%	27%									•					•							
Jenkins et al[32b]	149	NR		42%	25%									•											•	
Ohlsson et al[21]	111	18% postop	25	37%	25%							•		•							•	•	•			
Cady et al[25]	244	NR										•				•									•	
Bakalakos et al[20]	238	100% postop	23														•								•	
Kokudo et al[40]	132	57% postop		57%	42%								•					•		•						•
Harms et al[38]	245	65% postop	35										•							•					•	
Fong et al[10]	1001	NR	42	57%	37%			•				•	•	•		•		•							•	
Ambiru et al[22]	168	62% postop	23	42%	26%			•								•									•	•
Iwatsuki et al[24]	305	67% postop			32%								•	•		•	•			•					•	
Harmon et al[30b]	121	NR	42		46%								•					•								
Bradley et al[31b]	134	50% postop		50%	36%											•										
Seifert et al[37]	120	NR	30		31%													•							•	
Choti et al[11]	226	52% preop	46	57%	40%							•										•			•	
Ercolani et al[14]	245	41% postop		53%	34%										•											
Mala et al[18]	146	0 postop	37		29%			•				•													•	
Kato et al[4]	585[a]	55% postop		53%	39%							•	•	•											•	

Table 3 (continued)

Author	*n*	Chemo	Median OS	3-year OS	5-year OS	Gender	Age	Primary node	Rectal tumor	Primary T	Primary stage	CEA	DFI	EHD	CLM volume	#	Bilobar	Size	Satellitosis	Portal nodes	Grade	DOS	Blood tx	Anatomic	Margin	Postop chemo
Hofmann et al[16,17]	597	NR			33%			•						•				•	•		•			•		
Laurent et al[23]	311	44% postop		53%	36%		•	•	•							•										
Nagashima et al[34]	151[a]	NR		56%[c]	49%[c]									•		•		•								
Nicoli et al[35]	228	42% postop			16%																					
Schindl et al[15]	307[a]	0		52%[c]	36%[c]						•	•		•		•										
Pawlik et al[9]	557[a]	60% postop	74	74%	58%											•		•								
Wei et al[8]	423	32% postop	53		47%		•									•		•							•	
Tanaka et al[39]	156	most postop		54%	43%													•			•					
Malik et al[8]	484	most postop			42%											•										
Tsai et al[7]	145	100% postop			41%																					
Figueras et al[6]	545	65% postop[d]	44	60%	42%									•		•										•
Jonas et al[5]	685	35%[e]			37%											•				•		•			•	
Minagawa et al[2,3]	598[a]	NR		52%[c]	38%[c]			•				•				•				•						
Niu et al[1]	415	45% postop	32	45%	29%							•		•				•			•					
Parks et al[41]	792[a]	46% postop	41	55%	33%												•								•	•
This study	230	50%[f]	42	55%	38%			•				•														•

OS overall survival after hepatic resection, *Median* median overall survival after hepatic resection reported in months, *Chemo* percentage of patients treated with prehepatectomy or posthepatectomy chemotherapy, *CEA* carcino-embryonic antigen, *NR* not reported, # number of liver metastases, *Size* size of largest liver metastases, *DFI* disease-free interval from primary tumor resection to discovery or resection of liver metastases, *Primary node* node positive primary disease, *EHD* extrahepatic metastatic disease, *Bilobar* bilobar distribution of CLM, *Margin* positive/negative or width of hepatic resection margin, *Grade* grade of primary tumor or liver metastases, *Blood tx* intraoperative blood product transfusion, *Portal nodes* nodes in the hepatoduodenal ligament, *Anatomic* anatomic hepatic resection, *CLM volume* hepatic tumor volume, *DOS* date of hepatic resection, *Satellitosis* satellite lesions around main CLM, *Postop chemo* posthepatectomy chemotherapy

[a] Multi-institutional study

[b] Multivariate analysis not performed

[c] Reported for test cohorts

[d] 19% received multiagent posthepatectomy chemotherapy and 18% received prehepatectomy chemotherapy

[e] 35% received pre- or posthepatectomy chemotherapy; 12% received multiagent chemotherapy

[f] 50% each received pre- and posthepatectomy chemotherapy; 35% and 32% received multiagent chemotherapy

evaluation and comparison of particular drug combinations and treatment durations, the lack of a single standard chemotherapy schedule is representative of the current clinical treatment environment for patients with resectable CLM. This is despite the results of the EORTC phase III study, which demonstrated a progression-free survival benefit to a particular drug regimen (FOLFOX4) relative to observation.[47] Indeed, the variety of treatment schedules before and after resection of CLM observed at our institution are similar to that found at most other high-volume hepatobiliary centers.[1,4,5,9,11,12,14,21,23,26,27,31,39] Thus, the results of our study are likely applicable to the experience at most other institutions. Any improvement in long-term outcomes due to posthepatectomy HAI relative to systemic fluoropyrimidine alone (which was not significant in this study) would bias our results in favor of post-hepatectomy fluoropyrimidine-based chemotherapy. Despite this bias, multivariate analysis demonstrated a significant association with posthepatectomy multiagent chemotherapy. However, benefits of multiagent chemotherapy relative to that of systemic fluoropyrimidine therapy suggested by our study cannot be extended to HAI therapy as too few patients were treated with posthepatectomy HAI to make direct comparisons with posthepatectomy multiagent chemotherapy.

There are several limitations to our study. Retrospective data collection and analysis raises the possibility of selection bias confounding the association between chemotherapy and survival benefit. As patients were identified from a hepatectomy database, subjects who did not undergo hepatic resection because of tumor progression during chemotherapy were not examined. Duration of postoperative chemotherapy treatment was associated with overall survival in a multivariate analysis. However, we were not able to ascertain whether this reflected the total amount of chemotherapy administered or prolonged intervals between treatment cycles to recover from chemotoxicity. Due to the retrospective nature of this study and because posthepatectomy chemotherapy was not administered at our institution for many of the patients in this study, we were not able to assess whether morbidity after hepatic resection affected the decision to administer posthepatectomy chemotherapy. Because most patients administered posthepatectomy chemotherapy were treated within 2 months after hepatic resection, we could not determine the influence of a delay in starting posthepatectomy chemotherapy on overall survival. Although the year of partial hepatectomy did not affect long-term outcomes, enhancements in preoperative radiologic imaging, intraoperative ultrasound, and hepatic transection techniques after year 2000 may have contributed to the improved survival among patients treated with multiagent chemotherapy after hepatic resection. The relatively short length of follow-up after partial hepatectomy among patients treated with posthepatectomy multiagent chemotherapy may overestimate survival among these patients. Salvage treatments after disease recurrence, including additional resections of metastatic disease and additional chemotherapy regimens, may have also altered overall survival and were not considered in this study. These salvage treatments may have also been more frequently utilized in more recent years, thereby biasing results in favor of multiagent chemotherapy. While the size of our study is comparable to that of other retrospective series (Table 3), the relatively small number of patients with four or more CLMs, synchronous CLM (DFI=0), and large CLM may hinder our conclusions on the importance of postoperative multiagent chemotherapy and treatment duration relative to these clinicopathologic factors. Few patients in our series (n=3) had portal lymph node disease, a factor shown to be associated with poor survival after resection in some studies.[2,3,5,40] Because of these study limitations, we cannot make definitive conclusions concerning the benefits of multiagent chemotherapy compared to systemic fluoropyrimidine monotherapy or the duration and/or timing of chemotherapy relative to hepatic resection for CLM. Rather, this study provides the impetus for the design of prospective randomized controlled trials to adequately assess the benefits of multiagent chemotherapy compared to systemic fluoropyrimidine monotherapy for resectable CLM. Progression-free survival among those patients treated with posthepatectomy 5-FU/Leucovorin in the AURC 9002 trial was similar to that of patients treated with perioperative FOLFOX4 in the EPOC trial (3-year progression-free survival among resected patients 45% and 42%, respectively) with no overall survival benefit shown for either chemotherapy regimen relative to no chemotherapy.[46,47] While a study design that compares posthepatectomy chemotherapy to observation cannot be justified in the current era,[51] we do believe that a prospective randomized study comparing posthepatectomy systemic fluoropyrimidine and multiagent chemotherapy would be an important contribution to the overall multidisciplinary management of patients with CLM. This comparison would be an important extension of the prospective randomized trials comparing multiagent chemotherapy to systemic fluoropyrimidine therapy that have already been conducted for stage III and unresectable stage IV colorectal cancer.[42–44]

Based on the results of this single-centered retrospective study, posthepatectomy multiagent chemotherapy for at least 2 months in duration may have a survival benefit after resection of CLM. Markers of hepatic tumor burden classically associated with poor prognosis, including size and number of lesions, may be less relevant in the era of multiagent chemotherapy. Given these results and that of the EORTC 40983 phase III study, previous models used to estimate prognosis after hepatic extirpation that do not

factor treatment with multiagent chemotherapy regimens may not be relevant in the current era. Large, prospective randomized studies evaluating the effectiveness of multiagent chemotherapy for patients with resectable CLM are needed to validate the results of this retrospective, single-centered study.

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Impact of Adjuvant Gemcitabine Plus S-1 Chemotherapy After Surgical Resection for Adenocarcinoma of the Body or Tail of the Pancreas

Yoshiaki Murakami · Kenichiro Uemura · Takeshi Sudo · Yasuo Hayashidani · Yasushi Hashimoto · Hiroki Ohge · Taijiro Sueda

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Abstract
Background Few patients with pancreatic body or tail carcinoma are candidates for surgical resection, and the efficacy of postoperative adjuvant chemotherapy for patients with pancreatic body or tail carcinoma has not been elucidated. The aim of this study was to determine the effect of adjuvant gemcitabine and S-1 therapy for patients with adenocarcinoma of the body or tail of the pancreas who had undergone surgical resection by distal pancreatectomy.
Materials and Methods Medical records of 34 patients with pancreatic body or tail carcinoma who underwent surgical resection were reviewed retrospectively. Eighteen patients received postoperative adjuvant gemcitabine and S-1 chemotherapy. Univariate and multivariate models were used to analyze the effect of various clinicopathological factors on long-term survival.
Results There were no deaths due to surgery. Overall, 1-, 2-, and 5-year survival rates were 69%, 40%, and 25%, respectively (median survival time, 14.4 months). Univariate analysis revealed that adjuvant gemcitabine plus S-1 chemotherapy, blood transfusion, splenic artery invasion, lymph node metastasis, surgical margin status, and International Union Against Cancer stage were associated significantly with long-term survival ($P<0.05$). Furthermore, use of a Cox proportional hazards regression model indicated that adjuvant gemcitabine plus S-1 chemotherapy and absence of lymph node metastasis were significant independent predictors of a favorable prognosis ($P<0.05$).
Conclusion Postoperative adjuvant gemcitabine plus S-1 chemotherapy may improve survival after surgical resection for pancreatic body or tail carcinoma.

Keywords Pancreatic adenocarcinoma of the body or tail · Prognostic factor · Postoperative adjuvant chemotherapy · Gemcitabine · S-1

Introduction

Pancreatic carcinoma is one of the most aggressive types of gastrointestinal malignancies, and its prognosis remains extremely dismal.[1–10] The only chance for cure or long-term survival is surgical resection because chemotherapy and radiotherapy are not adequately effective. For complete tumor resection, distal pancreatectomy with splenectomy is usually performed for patients with adenocarcinoma of the body or tail of the pancreas, while adenocarcinoma of the head of the pancreas requires pancreatoduodenectomy. However, due to the late appearance of clinical symptoms, candidates for surgical resection of adenocarcinoma of the pancreatic body or tail are extremely few.[11–13] Most patients with pancreatic body or tail cancer often present with infiltration of the surrounding organs or regional blood vessels and distant metastasis including the liver or peritoneum. Therefore, there have been few reports concerning surgical treatment for adenocarcinoma of the body or tail of the pancreas,[11–20]

Y. Murakami (✉) · K. Uemura · T. Sudo · Y. Hayashidani · Y. Hashimoto · H. Ohge · T. Sueda
Department of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
e-mail: mura777@hiroshima-u.ac.jp

and the efficacy of postoperative adjuvant chemotherapy for patients with pancreatic body or tail carcinoma have not been elucidated.[11,14,18]

Since 2003, postsurgical adjuvant gemcitabine plus S-1 therapy have been performed for patients with pancreatic body or tail cancer in our institution. S-1 is an oral anticancer drug, which consists of tegafur as prodrug of 5-fluorouracil (5-Fu), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo). CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-Fu, and maintains efficacious 5-Fu concentrations in plasma and tumor tissues. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-Fu in the gastrointestinal tract and reduces the serious gastrointestinal toxicity associated with 5-Fu.[21] The combination of gemcitabine and tegafur had a marked synergistic cytotoxic effect against a human pancreatic cancer xenograft model.[22] In addition, combination chemotherapy with gemcitabine and S-1 was reported to improve survival in unresectable[23] or resected[24] pancreatic carcinoma. The aim of this retrospective study was to determine the effect of adjuvant gemcitabine and S-1 therapy for patients with adenocarcinoma of the body or tail of the pancreas who had undergone surgical resection by distal pancreatectomy. Cases treated at a single institution were assessed with univariate and multivariate survival analysis.

Patients and Methods

Patient Population

Between January 1990 and December 2007, a total of 114 patients with invasive ductal carcinoma of the pancreas underwent surgical resection at the Department of Surgery, Hiroshima University Hospital. The patient population consisted of 75 patients who underwent pancreatoduodenectomy, 34 patients who underwent distal pancreatectomy, and five patients who underwent total pancreatectomy. Medical records for the 34 patients with adenocarcinoma of the body and tail of the pancreas who had undergone distal pancreatectomy were reviewed retrospectively. All patients underwent tumor resection with the aim of achieving cure and had a confirmed pathological diagnosis. Patients with pancreatic ductal adenocarcinoma derived from an intraductal papillary-mucinous neoplasm or a mucinous cystic neoplasm were excluded from this analysis.[25,26] Preoperative workup included ultrasonography, computed tomography, endoscopic retrograde pancreatography, and endoscopic ultrasonography to evaluate the local or distant extension of the tumors. Postoperative adjuvant chemotherapy was administered beginning in 2003 and was given to 18 patients. The regimen of adjuvant chemotherapy was reported previously.[24] Briefly, patients received adjuvant chemotherapy with ten cycles of gemcitabine plus S-1 every 2 weeks. Each chemotherapy cycle consisted of intravenous gemcitabine at a dose of 700 mg/m^2 on day 1 and orally administered S-1 at a dose of 50 mg/m^2 for seven consecutive days, followed by a 1-week pause of chemotherapy. All 18 patients who had undergone surgical resection after 2003 received postoperative adjuvant gemcitabine plus S-1 chemotherapy. Neither external beam radiation nor intraoperative irradiation was given to any of the patients during the study period.

Surgical Procedures

All patients with carcinoma in the pancreatic body or tail underwent distal pancreatectomy with splenectomy. If the tumor invaded the adjacent organs, including the left adrenal gland, the transverse colon, the left kidney, the celiac or common hepatic artery, and the portal vein, these structures were also resected. All 34 patients underwent dissection of the regional lymph nodes, which included the nodes along the common hepatic artery, splenic artery, left gastric artery, superior mesenteric artery, splenic hilum, and inferior margin of the pancreas. Additional dissection of the para-aortic lymph nodes was performed in 28 patients. Intraoperative pathological assessment of the proximal pancreatic margins was performed with frozen tissue sections. If the pancreatic margin was positive for cancerous cells, further resection of the pancreas was performed to the maximum extent possible.

Pathological Investigations

After tumor resection, hematoxylin and eosin staining was performed. All specimens were examined pathologically, and each tumor was classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma according to the predominant pathological grading of differentiation. Anterior serosal invasion, retropancreatic tissue invasion, splenic or portal vein invasion, splenic artery invasion, lymph node metastasis, and extrapancreatic nerve plexus invasion were all examined pathologically. Surgical margins were considered positive if infiltrating adenocarcinoma was present at the proximal pancreatic transection line or in the dissected peripancreatic soft tissue margins. The final stage of pancreatic carcinoma was examined pathologically according to the tumor–node–metastases (TNM) classification system of malignant tumors published by the International Union Against Cancer (UICC), sixth edition.[27]

Survival

Patients were followed regularly in outpatient clinics at 3-month intervals by undergoing a blood test, ultrasonography, and computed tomography for up to 5 years after surgery. Information on outcomes more than 5 years after surgery was collected by telephone or personal interview. For patients who died, survival time after surgery and cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded. Survival analyses on five clinical factors (gender, age, combined resection of the adjacent organs, blood transfusion, and use of adjuvant chemotherapy) and 11 pathological factors (tumor size, tumor differentiation, anterior serosal invasion, retropancreatic tissue invasion, splenic or portal vein invasion, splenic artery invasion, lymph node metastasis, extrapancreatic nerve plexus invasion, surgical margin status, UICC pT factor, and UICC stage) were performed with univariate and multivariate methods.

Statistical Analysis

Survival curves were constructed using the Kaplan–Meier method, and differences in survival curves were compared by univariate log-rank (Mantel–Cox) test. Factors found to be significant on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model. $P<0.05$ was considered statistically significant. Statistical analysis was performed with the Macintosh version of StatView (version 5.0; SAS Institute, Cary, NC, USA).

Results

The 34 eligible patients included 21 men and 13 women (median age, 65 years; range, 48–82 years), and 11 patients (32%) were more than 70 years old. Mean (±SD) operative time was 266±68 min. Mean (±SD) estimated blood loss was 1,180±930 mL. Ten patients (29%) required blood transfusion during the procedure. The left adrenal gland, part of the transverse colon, the left kidney, part of the portal vein, and the celiac and common hepatic artery were resected in seven, two, one, one, and two patients, respectively. No arterial reconstruction was performed for patients who underwent resection of the celiac and common hepatic artery.[20] No 30-day operative deaths occurred among the 34 patients. However, the morbidity rate was 32%. The leading postoperative complication was pancreatic fistula in six patients (18%). One patient with a pancreatic fistula developed an arterial hemorrhage from the placed drain due to rupture of the stump of the splenic artery, but the patient was treated with arterial embolization, and the pancreatic fistula resolved. The other five patients who had a pancreatic fistula were treated conservatively by leaving the drains in place, and the fistulae resolved. Other complications were chylous ascites in four patients and wound infection in one patient. However, no patients required further surgery.

Pathologically, tumors <2 cm in greatest diameter were found in only five patients (15%). Anterior serosal invasion, retropancreatic tissue invasion, portal or splenic vein invasion, splenic artery invasion, and extrapancreatic plexus invasion were identified in 22 (65%), 26 (76%), 16 (47%), 10 (29%), and 10 patients (29%), respectively. There were 20 tumors (59%) with lymph node metastasis and 14 (41%) without lymph node metastasis, and four patients (12%) had involvement of the para-aortic lymph nodes. Fifteen patients (44%) had positive surgical margins. Tumors were identified as well-differentiated adenocarcinoma in 13 patients (38%), moderately differentiated adenocarcinoma in 15 patients (44%), and poorly differentiated adenocarcinoma in six patients (18%). According to the TNM system, two (6%), three (9%), eight (24%), 19 (55%), and two patients (6%) were diagnosed with stage IA, IB, IIA, IIB, and III disease, respectively.

Overall survival rates for the 34 patients were 69% at 1 year, 40% at 2 years, and 25% at 5 years (median survival, 14.4 months; range, 2 to 61 months; Fig. 1). However, only one patient has survived for more than 5 years. The patient had a tumor <2 cm with a positive lymph node and received adjuvant gemcitabine plus S-1 therapy postoperatively. Of the 34 patients, 19 patients died at the time of this writing. Eighteen patients died of recurrent disease, and one patient died of another disease. Recurrence was identified in 20 patients. The leading recurrence site was the liver (13 patients). Other recurrence sites were the peritoneum (four patients) and local (three patients). Of four patients with the para-aortic lymph node

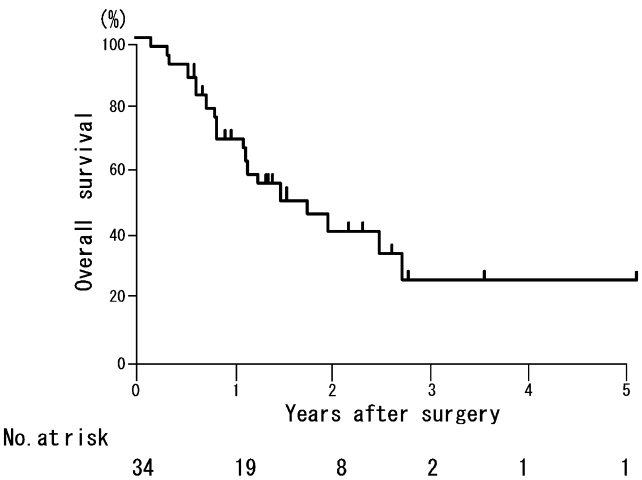

Figure 1 Overall survival in patients who underwent resection for adenocarcinoma of the body or tail of the pancreas.

involvement, three died of disease within 1 year, but one has remained alive without recurrence for 11 months.

Sixteen clinicopathological factors were investigated to determine their prognostic significance. The results of the log-rank test are shown in Table 1. Gender, age, combined resection of the adjacent organs, tumor size, tumor differentiation, anterior serosal invasion, retropancreatic tissue invasion, portal or splenic vein invasion, extrapancreatic nerve plexus invasion, and UICC pT factor did not influence postoperative survival by univariate survival analysis. In contrast, univariate analysis revealed that intraoperative blood transfusion (P=0.023), postoperative adjuvant chemotherapy (P<0.001), splenic artery invasion (P=0.020), lymph node metastasis (P=0.031), surgical margin status (P<0.001), and UICC stage (P=0.037) were associated significantly with survival (Table 1). These factors were entered into multivariate analysis with a Cox proportional hazards model, and use of postoperative adjuvant chemotherapy (P=0.004) and lymph node metastasis (P=0.013) remained independently associated with survival (Table 2). UICC stage was not used as a covariate variable in the multivariate survival analysis to avoid confounding with nodal status. Two-year survival rates of patients who did or did not receive postoperative adjuvant chemotherapy were 80% and 13%, respectively. All patients who did not receive adjuvant chemotherapy died of recurrence within 3 years after surgery (Fig. 2). Two-year survival rates of patients with or without nodal involvement were 21% and 65%, respectively (Fig. 3).

Table 1 Univariate Survival Analysis of Prognostic Factors for Patients with Adenocarcinoma of the Body or Tail of the Pancreas

Factors	Number of patients	2-year survival rate (%)	P value
Clinical factors			
Gender			
Male	21	40	0.595
Female	13	42	
Age (years)			
<70	23	40	0.659
≥70	11	39	
Combined resection of the adjacent organs			
Yes	10	45	0.636
No	24	37	
Blood transfusion			
Yes	9	11	0.023
No	25	56	
Adjuvant chemotherapy			
Yes	18	80	<0.001
No	16	13	
Pathological factors			
Tumor size			
<2 cm	5	80	0.185
≥2cm	29	35	
Tumor differentiation			
Well	13	43	0.743
Moderate, poor	21	37	
Anterior serosal invasion			
Yes	22	29	0.310
No	12	55	
Retroperitoneal tissue invasion			
Yes	26	39	0.275
No	8	44	
Portal or splenic vein invasion			
Yes	16	41	0.315
No	18	40	
Splenic artery invasion			
Yes	10	27	0.020
No	24	45	
Extrapancreatic nerve plexus invasion			
Yes	10	0	0.142
No	24	51	
Lymph node metastasis			
Yes	20	21	0.031
No	14	65	
Surgical margin			
Positive	15	13	<0.001
Negative	19	63	
UICC pT factor			
pT 1, 2	7	51	0.171
pT 3, 4	27	37	
UICC stage			
IA, IB	5	75	0.037
IIA, IIB, III	29	34	

P value is the result of a log-rank (Mantel–Cox) test.

Discussion

Few patients with pancreatic body or tail carcinoma are candidates for surgical resection.[11–13] Brennan et al.[13] reported that of 331 patients with adenocarcinoma of the body or tail of the pancreas, only 10% (34 patients) could undergo surgical resection. Another report found that of 513 patients with pancreatic body or tail carcinoma, 57 patients (11%) underwent resection with curative intent.[11] Moreover, of the total of resected pancreatic carcinomas that included pancreatic head carcinoma and pancreatic body or tail carcinoma, the rate of pancreatic body or tail carcinoma was reported to be only 3% to 18% in America and Europe,[5–10] although the rate was reported to be relatively high (27% to 35%) in Japan.[1–4] The resectability rate for body or tail lesions is extremely dismal, and therefore, the reported cases of resected pancreatic body or tail carcinoma are very few in the literature (22 to 88 patients, Table 3).[11–20]

Using multivariate analysis, several investigators have attempted to find useful prognostic factors for pancreatic carcinoma of the body or tail after surgical resection.[11,14,18]

Table 2 Multivariate Survival Analysis of Prognostic Factors for Patients with Adenocarcinoma of the Body or Tail of the Pancreas

Factors	Hazard ratio	95% CI	*P* value
Adjuvant chemotherapy			
Yes	1.0	2.1–49.3	0.004
No	10.2		
Lymph node metastasis			
Yes	4.3	1.4–13.8	0.013
No	1.0		

P value is the result of a Cox proportional hazards model.
CI Confidence interval.

According to these reports, potential factors include nodal involvement,[11,14] pathological grading of differentiation,[11] and portal or splenic vein invasion.[14] Shimada et al.[14] analyzed 88 patients with pancreatic body or tail carcinoma, and lymph node status and the degree of histologic portal or splenic vein invasion were independent predictors of long-term survival by multivariate analysis. Other authors reported that nodal involvement and poorly differentiated tumors were associated independently with poorer survival.[11] In the current analysis, blood transfusion, postoperative adjuvant chemotherapy, portal or splenic vein invasion, nodal involvement, surgical margin status, and UICC stage were identified as significant prognostic factors by univariate analysis. However, only administration of postoperative adjuvant chemotherapy and absence of nodal involvement were found to be independent favorable prognostic factors by multivariate analysis.

With regard to postoperative adjuvant therapy for patients with pancreatic carcinoma, several randomized controlled trials on a large number of patients demonstrated the usefulness of chemotherapy compared with chemoradiation therapy. A multi-center randomized trial conducted by the European Study Group for Pancreatic Cancer demonstrated that adjuvant chemotherapy using 5-fluorouracil plus leucovorin had a significant survival benefit compared with chemoradiation in patients with resected pancreatic carcinoma.[28] Recently, in a multi-center randomized controlled phase III trial (CONKO-001), Oettle et al.[29] reported that, compared with surgery alone, postoperative gemcitabine chemotherapy significantly delayed the development of recurrent disease after complete resection of pancreatic carcinoma. In addition, a meta-analysis of randomized adjuvant therapy trials for pancreatic carcinoma showed that chemotherapy, but not chemoradiation, was an effective adjuvant treatment for pancreatic carcinoma.[30] However, these effects were studied mainly in patients with pancreatic head carcinoma, and there have been no randomized controlled trials concerning the usefulness of chemotherapy for pancreatic body or tail carcinoma. Shimada et al.[14] reported that intraoperative radiation therapy or adjuvant chemotherapy with 5-Fu and cisplatin or gemcitabine did not influence the postoperative survival of pancreatic body or tail carcinoma. In the present study, we used a gemcitabine plus S-1 regimen as adjuvant chemotherapy for resected pancreatic body or tail carcinoma. Combination chemotherapy with gemcitabine and S-1 was reported to have survival benefits on patients with unresectable[23] or resected[24] pancreatic carcinoma. As a result, adjuvant gemcitabine plus S-1 therapy was an independent prognostic factor of long-term survival after surgical resection of pancreatic body or tail carcinoma in this series. We believe that this new adjuvant

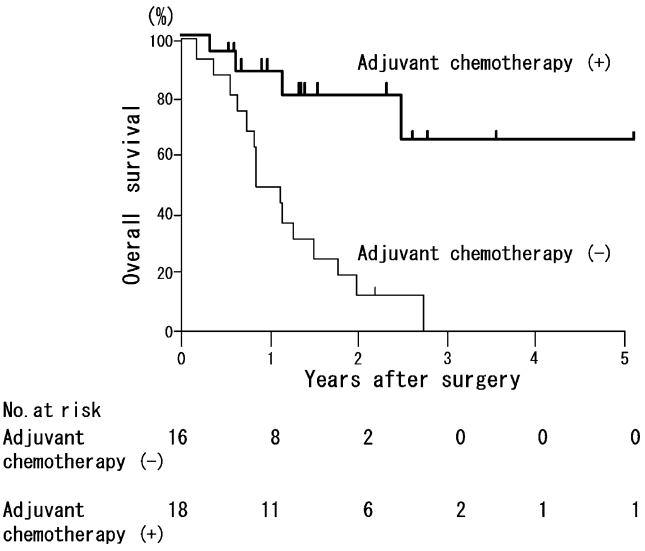

Figure 2 Comparison of postoperative survival in patients who did or did not receive postoperative adjuvant chemotherapy following resection for adenocarcinoma of the body or tail of the pancreas ($P<0.001$).

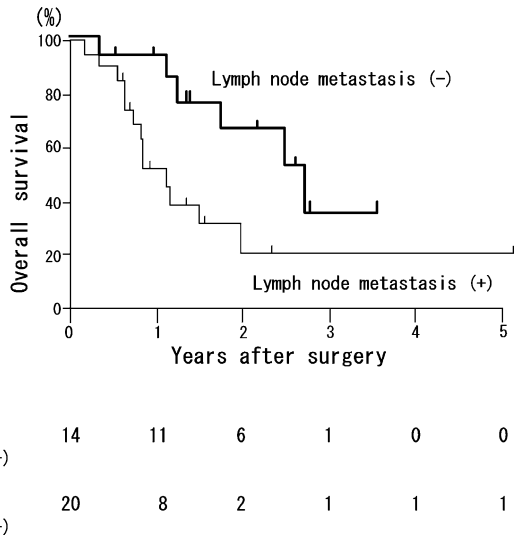

Figure 3 Comparison of postoperative survival in patients who underwent resection for adenocarcinoma of the body or tail of the pancreas, based on the presence or absence of lymph node metastasis ($P=0.031$).

Table 3 Recent Reports on Resectional Treatment of Adenocarcinoma of the Body or Tail of the Pancreas

Author	Year	Number of patients	Mortality (%)	Curative respectability (%)	Nodal involvement (%)	Median survival (months)	5-year survival rate (%)[a]	Prognostic factors by multivariate analysis
Our series	2008	34	0	56	59	14	25 (1)	AC, N
Hirano[20]	2007	23	0	91	65	21	41 (1)	NR
Strasberg[19]	2007	23	0	87	48	21	26 (1)	NR
Shimada[14]	2006	88	0	75	78	22	19 (7)	PV, N
Christein[18]	2005	66	2	83	30	16	10 (5)	None
Shoup[11]	2003	57	0	72	49	16	22 (6)	N, G
Sohn[15]	2000	52	2	80	59	12	15 (NR)	NR
Nakao[17]	1997	31	7	57	47	NR	10 (1)	NR
Sperti[12]	1997	24	8	67	25	11	13 (3)	NR
Brennan[13]	1996	34	0	68	47	12	14 (3)	NR
Ozaki[16]	1996	22	0	64	91	10	20 (4)	NR

AC Adjuvant chemotherapy, *PV* portal or splenic vein invasion, *N* nodal involvement, *G* pathological grading of differentiation, *NR* not reported
[a] Number in parenthesis indicates number of 5-year survivors.

chemotherapy contributes to long-term survival after surgical resection of pancreatic body or tail carcinoma. However, this study involved a small number of patients and was non-randomized. Randomized, prospective studies are needed to confirm the efficacy of adjuvant gemcitabine plus S-1 therapy for patients with pancreatic body or tail carcinoma.

Many reports have demonstrated by multivariate survival analysis that nodal involvement is related significantly to decreased survival in pancreatic head carcinoma.[2,7,9] Similar to these reports, lymph node status was also an independent predictor of long-term survival of pancreatic body or tail carcinoma in this series. Shoup et al.[11] and Shimada et al.[14] reported similar results that lymph node metastasis was one of the most important determinants of long-term survival in carcinoma of the body or tail of the pancreas, although another author found that nodal involvement did not influence survival.[18] Based on the results in our study and the previous reports, we believe that lymph node status is closely associated with long-term survival in pancreatic body or tail cancer, similar to the situation in pancreatic head carcinoma.

Several surgeons have utilized an extended distal pancreatectomy, which includes resection of the surrounding organs, such as the left adrenal gland, the left kidney, the stomach, and the regional blood vessels, to improve the survival of patients with pancreatic body or tail carcinoma.[11,14,16,18–20] Hirano et al.[20] reported that a distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer offered a high R0 resectability rate, with a 5-year survival and median survival of 42% and 21 months, respectively. In addition, Strasberg et al.[19] reported a new extended modification of distal pancreatectomy for adenocarcinoma of the body or tail of the pancreas, with a 5-year survival and median survival of 26% and 21 months, respectively. However, others have described that extended distal pancreatectomy provided no clear survival benefit and was associated with increased morbidity.[11,18] In the present study, the combined resection of the adjacent organs was utilized only when the tumor was judged by surgeons to invade the adjacent organs. As a result, survival was similar between distal pancreatectomy with and without combined resection of the surrounding organs. We believe that if R0 resection can be achieved by extended surgery, extended resection should be performed. Further studies on a larger number of patients are needed to determine the usefulness of extended distal pancreatectomy.

The prognosis of pancreatic body or tail carcinoma is dismal. Many surgeons reported that the 5-year survival rates of patients with pancreatic body or tail carcinoma after surgical resection were 10% to 20% (Table 3). In our series, the 5-year survival rate was relatively high (25%) compared with the previous reports. Administration of adjuvant gemcitabine plus S-1 therapy may contribute to the relatively high survival in this study. However, this study was based on a small number of patients, and further studies on larger numbers of patients are needed.

Five-year survivors with pancreatic body or tail carcinoma are rare, compared with pancreatic head carcinoma.[2,15,31] According to the previous literature, only one to seven patients have been reported to survive for more than 5 years (Table 3).[11–20] Moreover, the 5-year survivors have been reported frequently to die of recurrent disease 5 years after surgery. Shoup et al.[11] reported that half of six 5-year survivors with pancreatic body or tail carcinoma died of recurrent disease within the next 5 years. In addition, Christein et al.[18] reported that of four 5-year survivors, three who experienced recurrence before the 5-year mark died of disease thereafter. Based on these reports, 5-year

survival in pancreatic body or tail carcinoma does not mean cure.[12] Careful follow-up is needed for 5-year survivors after the 5-year mark.

In conclusion, postoperative adjuvant gemcitabine plus S-1 chemotherapy may improve survival after surgical resection for pancreatic body or tail carcinoma. Nodal involvement indicates a poor prognosis for long-term survival. To improve long-term survival, postoperative adjuvant chemotherapy with gemcitabine and S-1 may be essential for patients with pancreatic body or tail carcinoma following surgical resection. Prospective randomized studies are required to confirm the usefulness of adjuvant gemcitabine plus S-1 chemotherapy for patients with pancreatic body or tail carcinoma.

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Predicting Strangulated Small Bowel Obstruction: An Old Problem Revisited

Tim Jancelewicz · Lan T. Vu · Alexandra E. Shawo · Benjamin Yeh · Warren J. Gasper · Hobart W. Harris

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Abstract
Background Diagnosing intestinal strangulation complicating a small bowel obstruction (SBO) remains a considerable challenge. Despite decades of experience and numerous studies, no clinical indicators have been identified that reliably predict this life-threatening condition. Our goal was to determine which clinical indicators in patients with SBO can be used to independently predict the presence of strangulated intestine.
Methods Medical records were reviewed for 192 adult patients operated on for acute SBO over an 11-year period (1996–2006). Seventy-two preoperative clinical, laboratory, and radiologic findings at admission were examined. Data from patients with strangulated intestine were compared to data from patients without bowel compromise. Likelihood ratios were generated for each significant parameter in a multivariate logistic regression analysis.
Results Forty-four patients had bowel strangulation requiring bowel resection, and 148 had no strangulation. The most significant independent predictor of bowel strangulation was the computed tomography (CT) finding of reduced wall enhancement, with a sensitivity and specificity of 56% and 94% [likelihood ratio (LR) 9.3]. Elevated white blood cell (WBC) count and guarding were moderately predictive (LR 1.7 and 2.8).
Conclusion Regression analysis of multiple preoperative criteria demonstrates that reduced wall enhancement on CT, peritoneal signs, and elevated WBC are the only variables independently predictive of bowel strangulation in patients with SBO.

Keywords Small bowel obstruction · Intestinal strangulation · Small intestine

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T. Jancelewicz · L. T. Vu · A. E. Shawo · W. J. Gasper · H. W. Harris (✉)
Department of General Surgery, University of California, San Francisco,
513 Parnassus Av. S320,
San Francisco, CA 94143, USA
e-mail: harrish@surgery.ucsf.edu

B. Yeh
Department of Radiology, University of California, San Francisco,
San Francisco, CA 94143, USA

Introduction

Intestinal strangulation is a feared complication of acute small bowel obstruction (SBO), with a mortality of up to 40% in some series.[1,2] Determining which patients require urgent operative management remains a significant challenge, due to the highly variable presentation and course of this disease. The identification of defined clinical criteria predictive of strangulated bowel in patients with SBO could allow decreased time to laparotomy and improved outcomes.

In 1962, a landmark study by Silen, Hein, and Goldman of 480 patients with SBO demonstrated that predicting bowel strangulation obstruction was next to impossible using any clinical variable or the radiograph.[3] Twenty years later, Zuidema revisited the problem with a prospective study and showed similar results; even the most experienced surgeons were unsuccessful at identifying intestinal strangulation with statistical confidence.[4] The present study

aims to readdress this issue by retrospectively examining a broad array of admission clinical, laboratory, and imaging findings in patients with acute SBO, in an attempt to identify independent predictors of strangulation. Recent work, largely in the radiology literature, has suggested that computed tomography (CT) is a reliable modality for the identification of ischemic bowel, with reported sensitivities of over 90% and a specificity of nearly 100%.[1,5–9] We propose that regression analysis of CT and clinical findings could allow the identification of predictive risk factors for small bowel strangulation in patients presenting with acute intestinal obstruction.

Methods

Patients and Study Design

Approval for this study was obtained from the institutional review board of the University of California, San Francisco (UCSF). Between January 1996 and December 2006, 1,624 patients were discharged from UCSF Medical Center with a primary diagnosis of small bowel obstruction due to any cause (previous operation, internal hernia, etc.). A retrospective chart review of these patients identified 192 who underwent exploratory laparotomy during their admission. Subjects under age 18 were excluded from analysis, as were patients with acute vascular (mesenteric) ischemia, large intestinal involvement, chronic bowel obstruction, or subacute (elective) presentation. Patients were then divided into two groups according to operative findings: group 1 included patients found to have strangulated small intestine requiring resection, and group 2 included patients who did not have strangulated bowel. Patients in group 2 had either lysis of adhesions or resection of viable bowel for reasons other than strangulation, such as serosal tears, adherent bowel, or stenosed but non-strangulated segments. "Strangulation", or transmural necrosis, was based on operative descriptions and confirmed with pathology reports where possible.

Preoperative data gathered included: age, sex, abdominal operative history, time to OR, relevant admission symptoms (abdominal pain, fever, vomiting, anorexia, etc.), admission vital signs, maximum preoperative temperature and heart rate, minimum preoperative blood pressure, use of vasopressors, recent history of immunosuppression (history of HIV, transplant, or chemoradiation therapy), all appropriate laboratory studies including hematologic, electrolyte, blood gas, and enzyme levels when available [amylase and lactate dehydrogenase (LDH)], and a range of physical exam findings by the admitting surgeon (rebound, guarding, tenderness, distention, etc.). Note was made of the documented indication for laparotomy (imaging findings, clinical progression, failure of nasogastric decompression, etc.). Plain film imaging reports were also recorded. Peri- and postoperative data recorded included intraoperative findings and procedures, pathology results, and patient outcome including death, reoperation if any, and time until discharge.

All preoperative abdominal CT scans were reviewed by a single attending radiologist (B.Y.) who was blinded to the operative findings. The studies were evaluated for the presence or absence of: dilated loops, ascites, thick-walled small bowel (>3 mm), segmental mesenteric fluid, free air, fat stranding, small bowel feces sign, reduced or non-enhancement, pneumatosis, transition point, or evidence of closed-loop obstruction or multiple transition points.

Outcome Measure

The main outcome examined was the presence of strangulated small bowel necessitating operative resection in patients with acute small bowel obstruction.

Statistical Analysis

Initial univariate analysis was done using chi-squared tests for categorical variables and the Wilcoxon rank sum test for continuous nonparametric variables. Multivariate analysis incorporated significant preoperative findings from the univariate analysis to determine the independent predictors of strangulated bowel. Likelihood ratios were used to assess variables determined to be significant by multivariate analysis. A P value less than 0.05 was considered significant.

Results

Patient Group Characteristics

Of 192 patients included in the study, 44 were found to have bowel strangulation at laparotomy and underwent small bowel resection (group 1, Table 1). One hundred patients underwent lysis of adhesions without bowel resection and 48 patients had bowel resection for reasons other than strangulation (total 148 patients, group 2, Table 1). While there was no statistical difference in age between groups (mean 61 years in group 1 vs. 57 in group 2), there were more females in group 1 (73% vs. 53%, $P<0.05$). A history of abdominal operation was present in 73% of group 1 and 93% of group 2 ($P<0.01$). Recent abdominal operation (<60 days postoperative) was present in 7% of patients in group 1 and in 13% of patients in group 2. Group 2 demonstrated a significantly longer time to operative intervention at a median of 2 days versus 1 day

Table 1 Select Patient Characteristics

	Group 1 (N=44) Strangulated SBO	Group 2 (N=148) Non-strangulated SBO
N (192 total)	44	148
Age (mean years±SD)	61.2±18	57.3±17
Female gender	32 (73%)	79 (53%) $P<0.05$
History abdominal operation	32 (73%)	138 (93%)
Presented <60 days postop	3 (7%)	19 (13%)
Preoperative CT scan	33 (75%)	110 (74%)
Imaging contributed to decision to operate	28 (64%)	118 (80%)
Median days to OR (IQR)	1 (0–3)	2 (0–10) $P<0.001$[a]
Median days to discharge (IQR)	8 (4–34)	10.5 (4–76) $P<0.05$[a]
In-hospital mortality	4 (9.1%)	0
Reoperation[b]	5 (11%)	5 (3%)

IQR interquartile range
[a] P values versus group 1
[b] Reoperation indicates return to the operating room for laparotomy during the index admission

for group 1 ($P<0.001$) and time to discharge at a median 10.5 days versus 8 days for group 1 ($P<0.05$). Reoperation (take-back or second-look laparotomy) occurred in very few patients (11% of group 1 and 3% of group 2). The highest postoperative mortality was seen in group 1, with four deaths (9.1%). There were no deaths in group 2.

A total of 143 (74%) patients underwent preoperative CT scan for which films were available for review. One hundred twenty-four patients (65%) had scans using intravenous (IV) contrast. It was not possible to assess for reduced bowel wall enhancement in the small group of patients (N=19) who were scanned but did not receive IV contrast.

Imaging results were cited by the surgeon as a reason to proceed to operation in 64% of patients in group 1 and 80% of patients in group 2. Other reasons patients underwent laparotomy were clinical deterioration, lack of clinical improvement with conservative management, history of multiple episodes of acute SBO, severe pain, or peritoneal signs.

A total of 33 preoperative clinical findings, 17 laboratory variables (at multiple preoperative timepoints), and 11 CT scan findings were recorded for each patient, of which most were used for univariate analysis (Table 2). For evolving vital signs and laboratory values occurring over the preoperative course (e.g., blood pressure decreasing or white blood cell count increasing), the "worst" value was used for analysis. Some parameters were present at very low frequency in the population, including LDH, lactate, amylase, guaiac testing, and arterial blood gases, and were omitted from analysis. Preoperative acidosis was considered an important potential indicator of bowel compromise and was therefore estimated using serum bicarbonate concentration, which was available in 100% of patients; acidosis was considered present if the lowest preoperative bicarbonate value was <20 mEq/l. Similarly, renal failure was defined as a creatinine >1.5 mg/dl or blood urea nitrogen to creatinine ratio of >20.

Univariate Analysis

Univariate analysis identified a number of parameters present at a higher frequency in patients with bowel strangulation (Table 2). No significant difference between groups was seen for any presenting symptom (e.g. abdominal pain, vomiting), and these are not included in the table.

By P value criteria, the most important objective clinical factors associated with small bowel strangulation were peritoneal signs and hypotension. Group 1 also had a significantly higher frequency of acidosis and a higher average white blood cell (WBC) count, and patients tended to be hyperglycemic and have a higher blood urea nitrogen (BUN). Patients with a history of abdominal operation or an elevated temperature at presentation had a significantly lower frequency of bowel strangulation.

Multiple CT scan findings were significantly more common in group 1, including ascites, thick-walled small bowel, segmental mesenteric fluid, fat stranding, reduced wall enhancement, and evidence of a closed-loop obstruction or multiple transition points. Virtually 100% of patients in both groups demonstrated small bowel diameter >3 cm and this was not a significant predictor of strangulation (data not shown), nor was evidence of a single transition point. The small bowel feces sign was also not present at a higher frequency with strangulation.

Multivariate Analysis

Since imaging findings were among the most significant variables in the univariate analysis, patients who did not have a contrast CT scan were excluded from multivariate analysis, yielding 120 patients for comparison (Table 2, right-hand columns). Nearly every variable proved insignificant in the logistic regression analysis, with the exception of reduced wall enhancement on CT scan with an odds ratio (OR) of 142.3 ($P<0.001$), WBC count >12,000/ml (OR 20.3, $P<0.005$), and guarding (OR 14.9, $P<0.005$). Different permutations of input variables in the analysis, such as the omission of clinical findings present at a low frequency in the population, changed the OR values to some extent; however, reduced enhancement, guarding, and elevated WBC count remained the only independent predictors.

Reduced enhancement was 56% sensitive and 94% specific for bowel strangulation [likelihood ratio (LR) 9.3, Table 3]. WBC >12,000/ml was 45% sensitive and 74% specific (LR

Table 2 Univariate and Multivariate (Logistic Regression) Analysis of Patients with Obstruction and Small Bowel Strangulation (Group 1) Versus Patients with Obstruction and no Strangulation (Group 2)

	Univariate analysis (N=192)			Multivariate analysis (N=120)	
	Group 1 (strangulation)	Group 2 (no strangulation)	P value	OR	P value
	N (%)	N (%)			
	Median (IQR)	Median (IQR)			
CT findings:					
Ascites	28 (87.5%)	67 (62.6%)	<0.01[b]		NS
Thick-walled small bowel	17 (51.5%)	30 (28.3%)	0.01[b]		NS
Segmental mesenteric fluid	20 (64.5%)	27 (25.7%)	<0.001[b]		NS
Free air	2 (6.5%)	1 (0.9%)	0.06[b]		NS
Fat stranding	26 (81.3%)	44 (41.5%)	<0.001[b]		NS
Small bowel feces sign	13 (41.9%)	29 (27.6%)	0.13[b]		NS
Reduced wall enhancement	14 (56%)	6 (6.1%)	<0.001[b]	142.3	<0.0001
Pneumatosis	5 (16.1%)	4 (3.8%)	0.02[b]		NS
Transition point	28 (93.3%)	89 (82.4%)	0.14[b]		NS
Closed loop	15 (48.4%)	21 (19.8%)	0.001[b]		NS
Clinical findings:					
Gender: female	32 (72.7%)	79 (53.4%)	0.02[b]	3.3	NS
Age (years)	65.5 (30–81)	58.5 (23–88)	0.13[a]		
Maximum temperature (F)	36.7 (36–38)	37.2 (36–38.9)	<0.001[a]		
Minimum SBP (mmHg)	90 (69–120)	91 (60–130)	0.9[a]		
Fever	10 (22.7%)	59 (40.1%)	0.04[b]		NS
Tachycardia	21 (50%)	72 (48.7%)	0.9[b]		NS
Hypotension	10 (23.3%)	11 (7.4%)	<0.005[b]		NS
Need for vasopressors	5 (11.4%)	2 (1.4%)	<0.005[b]	7.5	NS
Abdominal pain	40 (97.6%)	132 (95.7%)	0.6[b]		
Abdominal tenderness	34 (77.3%)	111(75%)	0.8[b]		
Abdominal distension	26 (59%)	95 (64.2%)	0.5[b]		
Guarding	17 (38.6%)	20 (13.5%)	<0.001[b]	14.9	0.003
Rebound	8 (18.2%)	8 (5.4%)	<0.01[b]		NS
Altered mental status	8 (18.2%)	5 (3.5%)	<0.001[b]		NS
Leukocytosis ($\times 10^3/\mu l$):					
WBC	11.6 (4.0–22.6)	8.8 (2.4–21.8)	<0.05[a]		
WBC: 5–12 (reference)	18 (40.9%)	76 (51.4)	<0.05[b]		
WBC: <5	6 (13.5%)	34 (23%)	–	0.2	NS
WBC: >12	20 (45.5%)	38 (25.7%)	–	20.3	0.004
Acute renal failure:					
BUN (mg/dl)	20 (10–65)	17 (5–63)	<0.05[a]		
creatinine (mg/dl)	1 (0.6–2.7))	1 (0.5–9)	0.5[a]		
BUN/cr	19 (9.3–48.3)	17.1 (5–35.6)	0.15[a]		
BUN/cr >20	18 (40.9%)	44 (29.7%)	0.2[b]		NS
cr >1.5	11 (25%)	21 (14.2%)	0.09[b]		NS
Other:					
Bicarbonate (mEq/l)	22 (13–28)	25 (16–35)	<0.001[a]		
Acidosis: bicarbonate <20	13 (29.6%)	10 (6.8%)	<0.001[b]		NS
Glucose (mg/dl)	145 (90–272)	122 (81–280)	0.01[a]		
Hematocrit (%)	39.8 (29.5–51)	40 (29.6–49.5)	0.6[a]		
Platelet ($\times 10^3/\mu l$)	262 (131–386)	256 (136–700)	0.9[a]		
Sodium (mEq/l)	137 (129–144)	137 (126–143)	0.5[a]		
Potassium (mEq/l)	3.9 (3.2–5)	4.1 (3.3–8.6)	0.2[a]		
Chloride (mEq/l)	100 (87–108)	99 (80–108)	0.2[a]		
Previous operation	32 (72.7%)	130 (89.0%)	<0.01[b]		NS
Immunosuppression	7 (16.7%)	33 (22.3%)	0.4[b]		NS

IQR interquartile range, *OR* odds ratio, *cr* creatinine, *NS* not significant

[a] Wilcoxon rank sum test for continuous variables

[b] Chi-squared test for categorical variables

Table 3 Sensitivity, Specificity, and Likelihood Ratios of Parameters Found in the Multivariate Analysis to be Significant Indicators of Bowel Strangulation

Findings	Sensitivity	Specificity	Likelihood ratio
CT: reduced enhancement only	56%	94%	9.3
Guarding only	39%	86%	2.8
WBC >12 only	45%	74%	1.7
WBC >12 and CT: reduced enhancement	20%	100%	Infinite
WBC >12 and guarding	18%	97%	6.0
Guarding and CT: reduced enhancement	16%	100%	Infinite
WBC>12, guarding, and CT: reduced enhancement	4%	100%	Infinite

1.7). Guarding was 39% sensitive and 86% specific (LR 2.8). Combinations of these findings led to 100% specificity and infinite LR, but had low sensitivity (Table 3).

Discussion

This study of 192 patients with small bowel obstruction demonstrates that it remains difficult to predict bowel strangulation in this population, as has been shown repeatedly over the past 40 years.[3,4,10–13] During that time, an enormous number of clinical and laboratory tests have become available to assist the general surgeon with diagnosis, and our data suggests that almost none of them should reliably contribute to preoperative decision making in this setting. However, the importance of CT scanning to the armamentarium of the contemporary surgeon cannot be over-emphasized, since the single most significant predictor of compromised bowel by multivariate analysis using dozens of preoperative criteria was reduced intestinal wall enhancement on contrast abdominal CT scan. Even in the absence of such classic findings as a high WBC count or peritoneal signs, we have shown that CT can independently indicate bowel strangulation with a specificity of 94%. The presence of other significant clinical factors, while adding to specificity, lowered sensitivity when combined with reduced enhancement on CT (Table 3), which implies the generation of a scoring system would not be useful due to the poor sensitivity of most variables. In fact, the most specific CT findings are not always identified in patients with strangulation. Also, patients may present with acute renal failure and therefore do not undergo contrast CT; indeed, 14% of patients with strangulation had non-contrast CT scans in our study.

In practice, a patient with bowel obstruction, obvious septic physiology, and peritoneal signs would likely undergo exploration without delay, irrespective of other findings such as laboratory or imaging results. Indeed, the sickest patients—namely, those with strangulation—demonstrated the most rapid time to operation in our study (1.2 days). Despite this, the vast majority of patients (approximately 80%) underwent preoperative CT scan, suggesting that there was still doubt regarding diagnosis or, presumably, interest on the part of the surgeon in confirming a diagnosis prior to laparotomy. It is also possible that CT scanning was ordered by the emergency room physician prior to surgical consultation in some cases, although this variable was not specifically investigated in the chart review. Imaging contributed to the decision to proceed to operation in the majority of cases, which further suggests that diagnostic uncertainty is the norm in patients with SBO, thereby leading the surgeon to obtain objective radiologic findings before deciding to explore the patient.

Several studies, largely in the radiology literature, have emphasized the ability of CT to predict which patients with acute bowel obstruction have strangulation or will ultimately require laparotomy.[6,14,15] A meta-analysis by Mallo et al. of 15 separate studies found CT to be 83% sensitive and 92% specific in selecting patients with ischemic bowel in the setting of SBO; importantly, in patients without evidence of complete obstruction on CT, resolution without operation occurred in more than 90% of patients [negative predictive value (NPV) >90%].[8] A limitation of the analysis is that specific CT findings were not addressed, but the authors suggest that a scoring system based on CT findings is perhaps warranted. Sheedy et al. have shown that decreased segmental enhancement is the most specific sign for small intestinal ischemia, but they also demonstrated

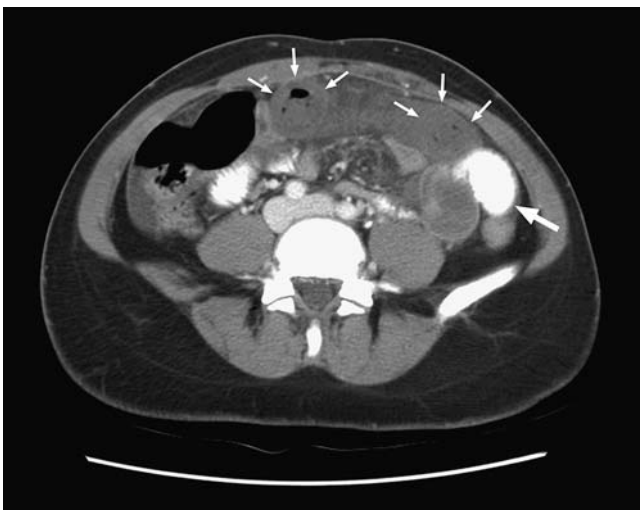

Figure 1 Representative CT scan demonstrating reduced small bowel enhancement and wall thickening (*small white arrows*) in a patient with SBO and strangulation. Note that the presence of dense oral contrast obscures the assessment of bowel wall enhancement in that segment (*large white arrow*).

that, despite CT consensus review by a separate radiologist, prediction of small bowel ischemia was relatively insensitive (52%).[9] In contrast, Zalcman et al. estimated a sensitivity for contrast CT scanning of 96% and an NPV of 99% for ischemia in the presence of SBO, also using consensus radiologist review; reduced enhancement was by far the most sensitive and specific finding.[7] In studies of CT findings in patients with SBO, reduced wall enhancement has been touted as the sine qua non of strangulation and intestinal ischemia, but its absence certainly does not rule out strangulation.[1,7,9,14–16]

Not surprisingly, univariate analysis revealed that, besides certain CT findings, a number of clinical variables were more common in patients with strangulated versus non-strangulated SBO, including signs of sepsis such as acidosis, hypotension, and elevated BUN (Table 2). However, these factors were not independent predictors on multivariate analysis, suggesting statistical interdependence. Interestingly, a history of previous abdominal operation was more frequent in patients without strangulation, suggesting that obstruction due to causes other than operative adhesions is somewhat more likely to lead to strangulation; however, this study is underpowered to directly address this issue.

We have found with regression analysis of multiple clinical variables that CT alone—and, specifically, reduced wall enhancement—emerges as a moderately sensitive indicator of which patients with SBO will require bowel resection. In addition, correlation with the clinical findings of peritonitis and leukocytosis improves the likelihood of strangulation, but very few patients fulfilled even two of these criteria (14 patients). Other groups have emphasized the value of CT scan primarily in the context of a vague clinical presentation, and correspondingly, the value of clinical findings in the context of an equivocal CT scan.[1,17]

One potential recommendation to draw from these observations is that a reasonable effort should be made to obtain an IV contrast-enhanced study in patients with SBO. If renal failure is present, the potential diagnostic benefit of contrast CT scan might warrant proceeding with scanning using renal protection protocols (*N*-acetyl cysteine, sodium bicarbonate, and isosmotic contrast). When strangulation is suspected, the radiologist can attempt to maximize the examination of bowel wall enhancement by avoiding oral contrast agents (except water) and concentrating on mural findings upon CT review with the surgical team. As shown in Fig. 1, the presence of dense oral contrast can obscure the assessment of intestinal wall perfusion.

This study is limited by its retrospective format and is only moderately powered, but is potentially useful in its demonstration that many purportedly valuable preoperative findings do not definitively indicate strangulated bowel in patients with SBO nor do patients with strangulation demonstrate any feature with 100% consistency. Many such findings, including some "classic" CT features of strangulated intestine, are present in patients with and without strangulation, and therefore are simply not specific enough to be useful in clinical decision making or in the generation of a potential risk-stratification scoring system.

Conclusions

In summary, we have reassessed the value of a comprehensive array of clinical, laboratory, and imaging criteria in the prediction of which patients with SBO will require exploratory laparotomy and resection for strangulated small bowel, and found with multivariate regression analysis that only reduced wall enhancement is sufficiently sensitive and specific (56% and 94%) in this regard. Elevated WBC count and peritoneal signs (guarding) are also significant variables, although less specific. Reduced wall enhancement on CT scan is virtually diagnostic of strangulation, and hence a contrast study is the most useful modality in patients with SBO. Of course, clinical deterioration or non-progression with abnormal clinical findings such as peritonitis or leukocytosis should lead to operation despite an equivocal imaging study.

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Outcome of Right Colectomy for Cancer in Octogenarians

Anne J. Gurevitch · Baruch Davidovitch · Hanoch Kashtan

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Abstract
Background Colorectal cancer is one of the commonest malignancies in the elderly and, as such, is a major cause of morbidity and mortality. There is no consensus yet if age itself is a risk factor for adverse outcome after colectomy. The aims of the study were to evaluate the impact of age on operative results of right colectomy for cancer and to define factors that influence the postoperative mortality in octogenarians.
Methods Data of all patients who underwent right colectomy for colon cancer between January 2001 and December 2006 were collected retrospectively. Patients were divided into two groups: those who were 80 years and older and those who were less than 80 years old. Analysis included patients' demographics, comorbidities, American Society of Anesthesiologists class, functional status, mode of presentation, stage of disease, length of hospital stay, postoperative morbidity, and mortality.
Results A total of 124 consecutive patients with right colon cancer were operated. Control group included 84 patients less than 80 year old. Study group included 40 patients 80 years or older. In Cox multivariate regression analysis, poor functional status and emergent surgery were independent factors for postoperative mortality.
Conclusions There was no significant difference in the outcome of elective right colectomy between elderly patients and their younger counterparts. Operative mortality of emergency surgery was significantly higher in octogenarians. Emergent setting and poor functional status are major risk factors for postoperative mortality.

Keywords Right colectomy · Octogenarians · Colorectal cancer · Elderly · Mortality

Introduction

Life expectancy in Western world is increasing and as a result, the elderly represent a rapidly growing sector in industrialized countries.[1,2]

Colorectal cancer (CRC) is one of the commonest malignancies in the elderly and, as such, is a major cause of morbidity and mortality. The proportion of elderly patients undergoing surgery for CRC is rising steadily, as surgical resection remains the primary therapy whenever possible, either for cure or to avoid late complications, such as obstruction or perforation.

Elderly patients are considered to be a different population group compared to younger patients because of higher incidence of comorbidity, poorer functional status, and increased likelihood to present with more advanced disease and as emergency.

Some authors have shown that the effectiveness of treatment of colonic cancer in the elderly is similar to that of younger patients.[3–6] Nevertheless, there is no consensus yet if age itself is a risk factor for adverse outcome after colectomy.

In this study, we attempted to decrease the surgical variability by limiting our study population only to patients

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A. J. Gurevitch · B. Davidovitch · H. Kashtan (✉)
Department of Surgery B, Kaplan Medical Center,
POB 1, Rehovot 76100, Israel
e-mail: hkashtan@clalit.org.il

A. J. Gurevitch · B. Davidovitch · H. Kashtan
Hebrew University School of Medicine,
Jerusalem, Israel

who had right colectomy as a procedure that anatomically is well defined. The phenomenon of proximal migration in the distribution of colon cancer is consistent with recent literature,[7,8] and as a result, right colectomy is one of the most common types of resection. However, there are no studies addressed the outcome of right-side colonic resection in elderly.

The aims of the study were (a) to evaluate clinical manifestations of right-side colon cancer as compared to younger patients, (b) to evaluate the impact of age on operative results of right colectomy for cancer, and (c) to define factors that influence the postoperative mortality in elderly patients.

Patients and Methods

Data of all patients who underwent right colectomy for colon cancer at the Department of Surgery, Kaplan Medical Center between January 2001 and December 2006 were collected retrospectively.

Patients were divided into two groups: a study group of those who were 80 years and older and a control group of patients who were less than 80 years old. Analysis included patients' demographics, comorbidities, American Society of Anesthesiologists (ASA) class,[9] functional status, mode of presentation, stage of disease, length of hospital stay, and postoperative morbidity and mortality.

Right colectomy was defined as any resection extending from the cecum to, but without, the splenic flexure. Resections were designated as emergent in patients who had been admitted with obstructed or perforated right colon cancer and were operated within 24 h of admission. Primary anastomosis was performed in all patients. Postoperative complications were classified as major surgical complications and major general complications, including infectious complications. Major surgical complications were defined as anastomotic leakage or any complication required relaparotomy. Major general complications included cardiovascular complications (myocardial infarction, cardiac rhythm disturbances, heart failure, cerebral infarction, or pulmonary embolism), respiratory failure, or renal failure. Infectious complications included pneumonia and sepsis.

Postoperative mortality was defined as any in-hospital death or death occurring within 30 days after operation. Patients preoperative functional status was assessed using Karnofsky Performance Status Scale[10] and defined as poor when Karnofsky score was equal or below 40, i.e., patient who is unable to care for himself; requires equivalent of institutional or hospital care.

Data was analyzed using an "Statistical Package for the Social Sciences" (version 11 for Windows) statistical program. All statistical evaluations were carried out in an explorative sense. The chi-square or Fisher exact tests were used for comparison of categorical variables between the groups. Cox multivariate analysis was used to identify independent factors for postoperative mortality.

Results

A total of 124 consecutive patients with right colon cancer were operated.

Study group included 40 patients who were 80 years or older (median age 83.4, range 80–94). Control group included 84 patients who were less than 80 year old (median age of 68.6, range 39–79).

A comparison of preoperative data of both groups is summarized in Table 1.

The incidence of comorbidities was significantly higher among the elderly patients (80% and 55% respectively, $p<0.01$). Nine patients (23%) in the elderly group were classified as ASA score 3–5 as compared to six patients (7%) in the younger patients' group ($p<0.01$). Thirty-two percent of patients in the elderly group had poor functional status as compared to 8% in the younger group ($p<0.05$). Emergency surgery was performed in 30% of elderly patients compared to 9.5% in the younger group ($p<0.01$). There was no difference between the groups in tumor stage at presentation.

The overall postoperative mortality rate was 10% in the elderly group and 3.5% in the younger cohort ($p<0.01$). In the elderly group, all mortality cases were in emergency setting. In the younger cohort, two mortality cases were in emergency setting and one death occurred after elective surgery because of acute myocardial infarction.

Postoperative major complications were recorded in 27.5% in the elderly cohort compared with 17.8% in the younger group (NS), although general complications (pulmonary, cardiovascular, and urinary infection) were more frequent in the elderly (Table 2). There was no

Table 1 A Comparison of Patients Characteristics Between Study Group (Patients 80 Years and Older) and Control Group (Patients Less Than 80 Years Old)

	Control group age<80	Study group age≥80	*p* value
N	84	40	
Median age (range)	68.6 (39–79)	83.4 (80–94)	
M/*F* ratio	1	1.08	NS
Comorbidities	46 (55%)	32 (80%)	0.0001
ASA score 3–5	6 (7%)	9 (23%)	0.0001
Poor Functional status	7 (8%)	13 (32%)	<0.05
Emergency Surgery	8 (9.5%)	12 (30%)	<0.001
Stage C of disease	25 (29.7%)	13 (32%)	NS

Table 2 A Comparison of Postoperative Morbidity and Mortality Between Study Group (Patients 80 Years and Older) and Control Group (Patients Less Than 80 Years Old) Using Univariate Analysis

	Control Group	Study Group	p value
Hospital stay (days mean±SD)	7.6±2.2	7.5±3.8	NS
Postoperative mortality	3 (3.5%)	4 (10%)	0.001
Postoperative complications			
Pulmonary	2 (2.4%)	2 (5%)	
Cardiovascular	1 (1.2%)	2 (5%)	
Urinary tract infection	2 (2.4%)	2 (5%)	
Surgical site infection	5 (5.9%)	1 (2.5%)	
Sepsis	2 (2.4%)	1 (2.5%)	
Burst abdomen	0	1 (2.5%)	
Small bowel obstruction	3 (3.6%)	2 (5%)	
Total	15 (17.9%)	11 (27.5%)	NS

anastomotic leak requiring reoperation or demonstrated on CT scan.

The influence of age, tumor stage, ASA grade, comorbidities, emergency operation, and functional status on postoperative mortality were evaluated using multivariate Cox analysis. Emergent setting and poor functional status, but not age by itself, have been identified as independent risk factors for postoperative mortality (Table 3).

Discussion

CRC, the third leading cause of cancer death worldwide, represents 10% of cancer diagnoses and deaths.[11] CRC is primarily a disease of the elderly.[12] Age is a major risk factor for the development of CRC, with the incidence of carcinomas increasing with advanced age.[13]

Western population is aging, and as a result, there is a rapidly expanding cohort of octogenarians. Therefore, the medical and societal burdens of CRC will only worsen over the coming decades.

Elderly patients form a highly heterogeneous group. Their general physical status varies, and numerous comorbidities are common. Some studies report age to be an independent predictor of poor outcome in patients with CRC.[14,15] As a matter of fact, the relationship of age to outcome after surgery for CRC is complex and multifactorial.

Previous studies have demonstrated an age-related right shift of CRC.[7,13,16] Thus, the incidence of right-side colon cancer is increasing with age.

Current studies designated to evaluate outcome of colorectal surgery in aged population include patients undergoing operations for both right and left colon malignancies. Our study is dedicated solely to outcome of right colectomy.

Some studies have found that the older the patient at the time of surgery, the more advanced the tumor stage is likely to be.[17] This study has not revealed any significant difference in tumor's stage between the groups. However, acute presentation because of obstruction or perforation was more frequent in the elderly group, with emergency surgery performed in 30% of elderly patients compared to 9.5% in younger cohort, similar to previous studies reports.[18,19] This may be attributed to the shift of cancers to the right in older patients, which might contribute to delay in presentation and diagnosis. This speculation along with the observation from other studies that the elderly apply late for medical help[20,21] only emphasizes the importance of screening colonoscopy. Other CRC tests, such as virtual colonoscopy or stool-based molecular testing, have the potential to become important screening tests for elderly in the future.[22]

Although ASA class is an important predictor of perioperative morbidity and mortality, our study has not found chronologic age or high ASA score to be an independent risk factor of mortality. These data come in line with other studies that found the functional status of the patient to be a better predictor of outcome after surgery for CRC, making ASA scoring alone too imprecise as an instrument for treatment decisions.

Postoperative morbidity rate was higher in the elderly group (27.5% vs. 17.8%), but there was no statistical significance. Although major general complications were observed more frequently among the elderly group, specific surgical postoperative complications did not differ according to age. Primary anastomosis was done in all patients including those in emergent setting. As there was no evidence of anastomotic leak in our study, it appears that the present management of emergency right colectomy with primary anastomosis should continue to be the treatment of choice for obstructing or perforated carcinomas of the right colon. Thus, in surgical treatment of CRC in the elderly, the main problem is not surgery itself, but rather the preoperative and postoperative care which should be optimized to reduce the rate of postoperative complications and mortality.

Table 3 Cox Multivariate Analysis of Risk Factors Associated with Postoperative Mortality

Factor	Relative risk	*p* value
Age<80 vs. ≥80	1.384	0.16
ASA score 1–2 vs. 3–5	1.421	0.08
Emergency vs. elective surgery	3.971	<0.001
Normal vs. poor functional status	4.210	<0.001
Tumor stage C	2.279	0.11
Cardiovascular comorbidities	2.065	0.09
Pulmonary comorbidities	1.969	0.23
Renal comorbidities	1.480	0.15

Furthermore, thanks to advances made in surgical technique, anesthetic procedures, and postoperative medical care, modern surgery carries less risk for elderly patient.

Emergency surgery because of obstructed or perforated CRC in the elderly is associated with clearly higher postoperative morbidity and mortality rates than elective surgery.

Overall mortality was 10% in the elderly group, compared to 3.5% in younger patients. All mortality cases in the elderly group were in emergent setting. This finding comes in concordance with results of other studies that emphasize the strong negative influence of emergency surgery on the outcome.[23–25] The reason for this is the diminished physical status of the patient, and nonoptimal preoperative preparation of the patient. Therefore, physicians should see the uttermost importance in bringing the elderly patient to elective surgery.

Numerous studies have shown that the age-corrected survival rate of elderly patients is comparable with that of younger ones.[26–28] Thus, despite concomitant diseases that elderly patients may have, the cancer-specific survival after surgery seems to be similar to that of younger patients.

We recognize that there are limitations to this study design because of its retrospective nature, which may affect the validity of the conclusions. Our study is single institution, and therefore, the total number of patients is rather small, but we reduced some of the bias by choosing a homogenous group of right-side colon cancer only. Further prospective multi-center studies will provide a stronger validity to these findings.

Conclusions

There was no significant difference in the outcome of elective right colectomy between the elderly patients and their younger counterparts:

- Operative mortality of emergency surgery was significantly higher in octogenarians.
- Emergent setting and poor functional status are major risk factors for postoperative mortality.

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Health-Related Quality of Life after Colonic Resection for Diverticular Disease: Long-term Results

Marco Scarpa · Duilio Pagano · Cesare Ruffolo · Anna Pozza · Lino Polese · Mauro Frego · Davide F. D'Amico · Imerio Angriman

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Abstract
Background and Aims While colonic resection is standard practice in complicated colonic diverticular disease (DD), treatment of uncomplicated diverticulitis is, as yet, unclear. The aim of the present study was to evaluate the long-term clinical outcome and quality of life in DD patients undergoing colonic resection compared to those receiving medical treatment only.
Patients and Methods Seventy-one consecutive patients who were admitted to our surgical department with left iliac pain and endoscopical or radiological diagnosis of DD were enrolled in this trial. Disease severity was assessed with Hinchey scale. Twenty-five of the patients underwent colonic resection, while 46 were treated with medical therapy alone. After a median follow-up of 47 (3–102) months from the time of their first hospital admission, the patients responded to the questions of the Cleveland Global Quality of Life (CGQL) questionnaire and to a symptoms questionnaire during a telephone interview. Admittance and surgical procedures for DD were also investigated, and surgery- and symptoms-free survival rates were calculated. Nonparametric tests and survival analysis were used.
Results The CGQL total scores and symptom frequency rate were found to be similar in the two groups (resection vs nonresection). Only current quality of health item was significantly worse in patients who had undergone colonic resection ($p=0.05$). No difference was found in the rate and in the timing of surgical procedures and hospital admitting for DD in the two groups. In particular, the nine patients classified as Hinchey 1 who underwent surgery reported the same quality of life, symptoms frequency, operation, and hospital admitting rate as those who had been admitted with the same disease class but who received medical treatment only.
Conclusions Our results indicate that there does not seem to be any long-term advantage to colonic resection which should be considered only in patients presenting complicated DD.

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M. Scarpa (✉)
Department of Surgery, Veneto Oncological Institute (IOV-IRCCS), Clinica Chirurgica I, Policlinico Universitario,
via Giustiniani 2,
35128 Padova, Italy
e-mail: marcoscarpa73@yahoo.it

D. Pagano · C. Ruffolo · A. Pozza · L. Polese · M. Frego · D. F. D'Amico · I. Angriman
Clinica Chirurgica I, Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Policlinico Universitario,
Università di Padova,
via Giustiniani 2,
35128 Padua, Italy

Keywords Quality of life · Colonic diverticular disease · Colonic resection

Background

Diverticular disease (DD) of the colon is common in the Western world, accounting for more than 200,000 hospitalizations annually, health care costs of more than $300 million, and with a prevalence of approximately 33% in patients over 60 years of age.[1,2] Perforation associated with diverticular disease has concurrently increased in prevalence from 2.4 cases per 100,000 in 1986 to 3.8 cases per 100,000 in 2000.[3]

Colonic resection is standard practice when there is perforation and peritonitis. Primary anastomosis with defunctioning stoma seems to be the optimal surgical strategy for fit patients with diverticular peritonitis as it seems to be a good compromise between postoperative complications, long-term quality of life, and risk of requiring permanent stoma. Hartmann's procedure is, instead, recommended in high-risk patients.[4]

Treatment of acute diverticulitis without perforation and peritonitis is yet unclear. In these cases, nonoperative management is usually successful,[1,5] but up to 25% of these patients may end to require an urgent operation,[6] and more than half of these procedures involve a colostomy.[7–9] Elective colectomy is, thus, often recommended to avoid the risks and high mortality rate connected to emergency surgery usually associated with recurrent diverticulitis. The timing of elective surgery is, nevertheless, controversial, with most advisory bodies recommending surgery after the second episode.[1,10] Many surgeons, however, advise prophylactic colon resection after a single hospitalization in younger patients because the disease is considered more virulent in these subjects.[10–13] Advances in laparoscopic colonic surgery have widened the spectrum of indications, and a large multicentric study has recently reported that 87% of the patients undergoing this procedure are affected with an uncomplicated DD.[14]

The aim of the present study was to evaluate the impact of colonic resection for DD on the natural history and on the long-term quality of life of these patients. The study was particularly focused on the long-term clinical outcome of noncomplicated diverticulitis.

Patients and Methods

Patients

The hospital records as well as the clinical and surgical follow-up files of 149 consecutive patients who had been admitted to the Department of Surgical and Gastroenterological Sciences of the University of Padova from 1998 to 2005 with a diagnosis of DD were reviewed. Attempt was made to contact all of these, and the 71 who agreed to submit to a telephone interview were enrolled in our cross-sectional study. Healthy, normal subjects were also enrolled as controls.

The diagnosis of diverticular disease was based on a report of a barium enema, a colonoscopy, or both. At admission, all patients with left iliac fossa pain underwent plain abdomen X-ray and ultrasound (US) or computed tomography (CT) scan, and Hinchey 4-stage classification was used to assess severity of DD.[15] Hinchey stage 1 indicates acute phlegmonous diverticulitis without complications; Hinchey stage 2 diverticulitis with paracolic abscess without perforation; Hinchey stage 3 diffuse purulent peritonitis; and Hinchey stage 4 diffuse fecal peritonitis. Patients with no sign of perforation were conventionally classified as Hinchey 0.

Patients with Hinchey stage 2, 3, or 4 DD were treated with antibiotics, laparotomy, colonic resection, and if necessary, diverting stoma; the minimally invasive approach with percutaneous CT or US-guided drainage was always attempted to manage Hinchey stage 2 patients; subjects with nonperforated DD and Hinchey stage 1 DD were treated with antibiotic therapy, while colonic resection was considered whenever the patient reported more than two previous episodes of acute DD or in case of inflammatory stenosis.

Quality of life was also assessed in 69 healthy subjects [39 males and 30 females with a mean age of 43 (22–85) years] without gastroenteric symptoms enlisted from among hospital employees and their relatives

Study Design

Patients were enrolled in the study provided that they were admitted for abdominal pain, obstruction, or rectal bleeding and a confirmed diagnosis of diverticular disease. They were included in the medical group if they were treated with medical therapy and in the surgical group if they had a colonic resection. Patients also presenting other bowel diseases associated to Crohn's disease such as colon cancer were excluded. The study was conducted in accordance with the principles to Helsinki Declaration contacted by phone, all of the patients were provided information about the methods and the study's purposes, and those agreeing to give informed consent and to submit to a telephone interview were enlisted.

The long-term outcome of DD patients who underwent colonic resection or who were treated with medical therapy was compared. The outcome measures analyzed were: readmission to the hospital and/or further surgery for DD, current health status (fever, abdominal pain, constipation, diarrhea, rectal bleeding, and bloating), and quality of life. Each of these parameters was analyzed according to possible predictors such as gender, age at admission, symptoms at admission (fever, abdominal pain, constipation, diarrhea, rectal bleeding, and bloating), Hinchey disease severity class, indication for surgery, laparoscopy/laparotomy approach, the need of a diverting stoma, postoperative surgical and intestinal complications, co-morbidity, and medical therapy.

Italian Cleveland Global Quality of Life Questionnaire

The Cleveland Global Quality of Life (CGQL) score consists in three items (current quality of life, current quality of health, and current energy level), each on a scale of 0 to 10 (0, worst;

10, best). The scores were added, and the final CGQL utility was obtained by dividing this result by 30.[16] The CGQL was created to assess health-related quality of life (HRQL) in patients affected by ulcerative colitis after restorative proctocolectomy and then was used in HRQL analysis of patients with Crohn's disease.[17,18] Given its short framework, the Italian translation, recently validated in one of our previous studies,[19] was considered a suitable instrument for telephone interviews.

Surgical Technique

In open colonic resection, the exploration of the abdomen, the mobilization of the colon, the identification of the critical structures, the section of the vascular pedicle, the resection of the diseased colon, and the anastomosis were performed through a xifo-pubic midline incision. The extension of the resection was decided intraoperatively depending on the involved tract: it could be a simple sigmoidectomy or a proper left hemicolectomy with full mobilization of the splenic flessure. In any case, the resection was carried down to the level of the rectum at or just below the peritoneal reflection. A colon–rectal anastomosis was performed with a circular stapler (typically a CEEA 31) using end-to-end technique. The decision to open a diverting stoma was made intraoperatively, depending on the disease severity (Hinchey stage 3 or stage 4) and on the technical difficulty in creating the anastomosis.

In the laparoscopy-assisted colonic resection, open laparoscopy through a paraumbilical incision was used to obtain pneumoperitoneum. Typically, a 10-mm port was placed on the right midclavicular line in the higher abdominal quadrant, a 10-mm port was placed slightly more medially on the supra-pubic line in the lower abdominal quadrant, and a 5-mm port was always placed in the left iliac fossa in order to provide adequate traction when mobilizing the left colonic flexure and the sigmoid colon. Just as in the open procedure, the resection was carried down to the level of the rectum at or just below the peritoneal reflection. The mobilized bowel was then exteriorized through a small median peri-umbilical or Pfannestiel incision, typically smaller than 6 cm, and a standard open technique was used for the resection and the anastomosis of the colon.

Conservative Therapy

Medical therapy protocol in case of DD included fasting and parenteral nutrition while abdominal pain persisted associated to antibiotic therapy for 10 days (ciprofloxacin 500 mg twice daily and metronidazole 500 mg three times daily). US- or CT-guided percutaneous drainage was attempted in case of isolated abdominal abscess, and endoscopic hemostasis was carried out when there was rectal bleeding. All patients were discharged with a diet enriched with fibers, 1.5 l of liquid per day, and paramomicin cycle (one spoon tris in die for a week per month).

Statistical Analysis

Data are presented as median and range or number of patients affected (%). Alpha (the probability of committing a type I error) was set at 0.05 (two-tailed), beta (the probability of committing a type II error) at 0.20, and *E*/SD (standardized effect size, expected effect size divided by standard deviation) at 0.50; the sample size of the study and control groups was calculated to be at least of 63 patients for two-tailed *t* test. Continuous data were compared with Kruskal–Wallis analysis of variance (ANOVA), in case of multiple comparisons, or with Mann–Whitney *U* rank test when appropriate. Fisher exact test was used to compare dichotomous variables. Correlations between Italian CGQL and possible HRQL predictors were explored with the Spearman correlation rank test. All the variables that resulted to be significant at the univariate analysis were included in a multiple regression model in order to identify the independent predictor of long-term HRQL.

Admission-free and reoperation-free survival were calculated using the Kaplan–Meier method with follow-up time (time at risk) beginning at initial discharge from hospital and ending at the hospital admission for DD, at reoperation for DD, or at last available follow-up, whichever came first. Data were considered complete when hospital admission for DD or reoperation for DD, respectively, occurred. Cumulative recurrence rates were compared using the log rank test according to dichotomous or dichotomized variables. All the variables that resulted to be significant at the univariate analysis were included in a multiple variable Cox proportional hazards model. A level of $p<0.05$ was considered significant.

Results

One hundred forty-nine patients were admitted to our surgical department with a diagnosis of DD from January 1998 to December 2005. After a median follow-up of 47 (3–102) months from hospital admission, 71 of them could be contacted, accepted to have an interview, and thus, were eligible for the study. The characteristics of the patients enrolled in the study are shown in Table 1.

The 78 patients who did not participate to the study were 38 men and 40 women, their median age was 67 (35–93) years, and 25 of them had surgery for DD. Twenty-five patients were admitted for Hinchey stage 0 DD, 30 for Hinchey stage 1 DD, 14 for Hinchey stage 2 DD, six for Hinchey stage 3 DD, and three for Hinchey stage 4 DD.

Table 1 Patient Characteristics

	Colonic resection	Medical therapy	*p*
Patients	25	46	
Gender (male)	8 (32%)	20 (43%)	0.447
Age at admission (years)	67 (39–84)	71 (32–87)	
Symptoms at admission			
Fever	9 (36%)	8 (17%)	0.090
Abdominal pain	20 (80%)	34 (74%)	0.771
Constipation	13 (52%)	19 (41%)	0.457
Diarrhea	4 (16%)	10 (22%)	0.756
Rectal bleeding	1 (4%)	3 (6%)	1.000
Bloating	6 (24%)	22 (48%)	0.074
Diverticulitis severity (Hinchey)			
0	0	26 (56%)	<0.001
1	9 (36%)	17 (37%)	1.000
2	13 (52%)	3 (6%)	<0.001
3	2 (8%)	0 (0%)	0.120
4	1 (4%)	0 (0%)	0.342

The patients who did not participate were not significantly different from those who were actually enrolled in the study.

In the study group, a colonic resection was performed in 25 patients (10 left hemicolectomy and 15 sigmoidectomy), while the remaining 46 were treated with medical therapy (fasting, parenteral nutrition, and antibiotic therapy). Therapy adopted in the two groups is shown in Table 2. The disease severity was different in the two groups: Hinchey stage 3 and 4 patients were all operated on, while patients with no signs of diverticular perforation (Hinchey stage 0) were all treated with medical therapy. Three patients with Hinchey stage 2 DD were treated conservatively with percutaneous drainage of the abdominal abscess and antibiotic therapy, while 13 of them underwent colonic resection. The Hinchey stage 1 class was equally distributed in the two groups: nine patients had colonic resection, and 17 were treated with medical therapy. Therapeutical choice according to DD severity is shown in Fig. 1.

As shown in Figs. 2 and 3, no significant difference was evidenced in the rate and in the timing of readmission and surgical procedures for DD in the two groups (p=0.957 and p=0.372, respectively) as well as in the total number of re-admission for DD [0 (0–3) vs 0 (0–2), p=0.576]. There was no significant difference, likewise, in hospital admission rate as well as in the total number of re-admission for DD [0 (0–2) vs 0 (0–1), p=0.235] in the 26 patients with Hinchey stage 1 DD between those who had been operated on and those who had been treated conservatively (p=0.609). Among all the possible predictors, only the extension of surgery was associated to readmission for DD: patients who had a simple sigmoidectomy had a cumulative readmission-free survival rate higher than those who had left hemicolectomy (after 5 years follow-up, 93% vs 54%, p=0.047). None of the other possible predictors seemed to be associated to reoperation.

As shown in Table 3, no significant difference was observed in terms of symptoms rate at follow-up between the patients treated with colonic resection and those who had medical therapy.

Quality of life analysis is outlined in Table 4. CGQL total score as well as the two items current quality of life and current energy level responses were similar in the two groups of patients and in the group of healthy subjects. Only the scoring on the current quality of health was significantly worse in patients who had undergone colonic resection (p=0.02). Similarly, in the Hinchey 1 sub-group, no significant difference in CGQL score (p=0.948), current

Table 2 Therapeutic Choices

	Colonic resection	Medical therapy
Patients	25	46
Laparoscopy	5 (20%)	NA
Complications	4 (16%)	1 (2,1%)
Stoma	6 (24%)	NA
Stoma type		
Colonstomy	5 (20%)	NA
Ileostomy	1 (4%)	NA
Stoma closure	5 (83,3%)	NA
Complication stoma closure	1 (incisional hernia)	NA
Endoscopic hemostasis	0	2 (4%)
Medical therapy at discharge		
Antibiotics	11 (44%)	15 (33%)
Diet	4 (16%)	5 (11%)
Laxative	8 (32%)	9 (19%)
Mesalazine	2 (8%)	8 (17%)
Probiotics	1 (4%)	6 (13%)

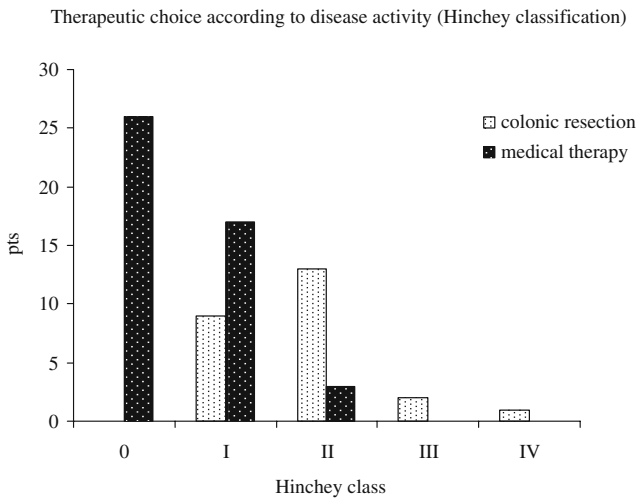

Figure 1 Distribution of therapeutic choices according to DD severity.

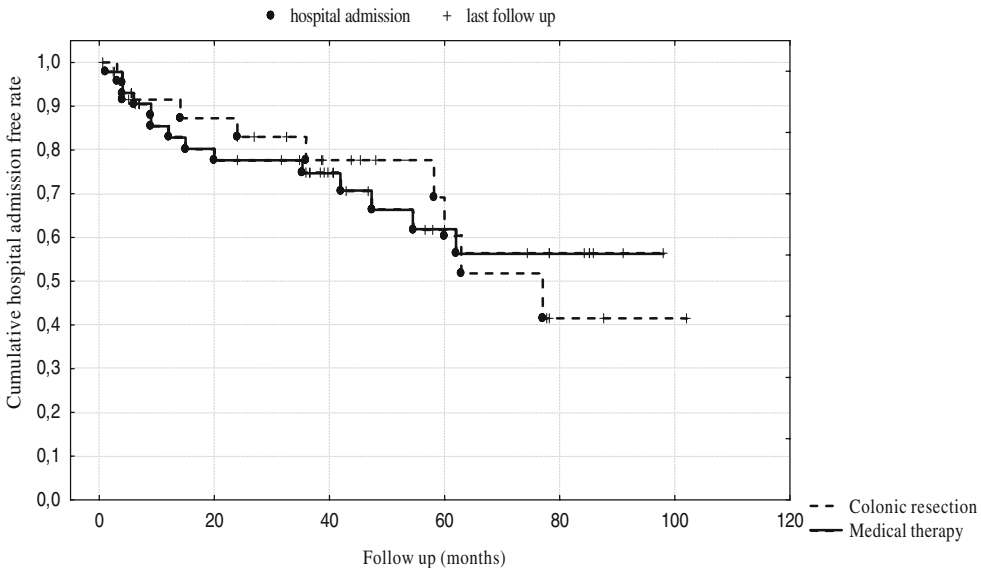

Figure 2 Cumulative hospital admission-free survival rate according to therapy.

quality of health (p=0.383), current quality of life (p=0.583) and current energy level (p=0.897) was observed in patients who had been operated on and those who had been treated conservatively. Patients' characteristics and long-term outcome of Hinchey I patients are summarized in Table 5.

Constipation at admission (R=−0.35, p=0.004), Hinchey severity class (R=−0.24, p=0.050), and antibiotic therapy (R=0.25, p=0.047) were significantly correlated with the CGQL score at univariate analysis, although none of these were confirmed independent predictors of quality of life at the multiple regression analysis.

Discussion

DD of the colon affects approximately one third of the population over 60 years of age in the Western world with a consequent impact on public health organization and costs,[1,2] and perforation associated with diverticular disease is the main complication.[3] In these cases, colonic resection is standard practice, but the management of episodes of uncomplicated diverticulitis is still unclear. Medical therapy is usually successful,[1,5] but the risk of emergency surgery,[6] often involving colostomy, must be considered.[7–9] Elective colectomy is often recommended instead of conservative

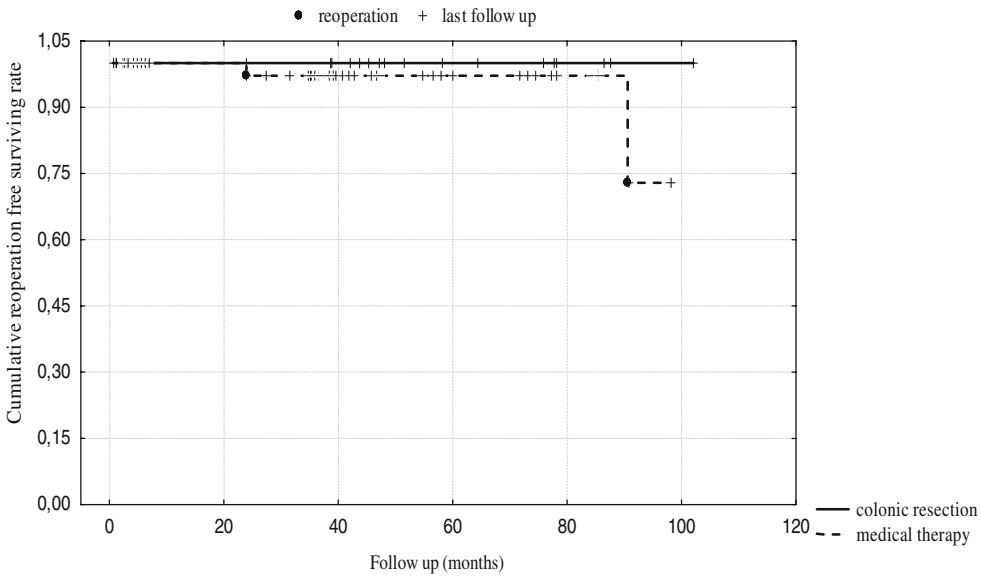

Figure 3 Cumulative reoperation-free survival rate according to therapy.

Table 3 Current Health Status

Symptoms at follow-up	Colonic resection	Medical therapy	*p*
Patients	23	44	
Fever	4 (17%)	5 (11%)	0.706
Abdominal pain	10 (43%)	19 (43%)	1.000
Stipsis	10 (43%)	14 (31%)	0.600
Diarrhea	4 (17%)	7 (15%)	1.000
Rectal bleeding	2 (9%)	1 (2. %)	0.545
Bloating	7 (30%)	17 (39%)	0.591

management to minimize these risks. Furthermore, the enthusiasm of surgeons for laparoscopic colonic surgery and its lighter impact perceived by the patients expanded the indications. Consequently, most of patients who have a laparoscopic colonic resection for diverticular disease have uncomplicated diverticulitis.[14] The biggest controversy today remains the management of recurrent and symptomatic chronic diverticular disease.[20] Therefore, the aim of the present study was to evaluate the impact of colonic resection for DD on the natural history and on the long-term quality of life of these patients.

Some authors reported that after one episode of DD treated conservatively, up to a third of patients develop recurrent symptoms, while recurrence rates after colonic resection for DD were between 1% and 10%.[21,22] On the contrary, in the present series, the rate and timing and total number of re-admissions for DD of the patients treated with conservative therapy and those who had a colonic resection was similar. This similarity in ratings was also observed in the group of patients with Hinchey stage 1 DD. This could be due, in part, to the lack of uniformity of definitions of episodes of diverticulitis in the different series.[20] In fact, many studies have reported that these patients are often affected with concomitant irritable bowel syndrome or that their recurrent symptoms in the immediate postoperative period may be related to anastomotic complications.[23] In the present study, episodes of diverticulitis were defined as left iliac fossa pain associated to fever or rise of serum inflammatory markers (white blood cell count, C-reactive protein or erythrocyte sedimentation rate).

Table 4 Health-Related Quality of Life in the Two Groups and in Healthy Controls

	Colonic resection	Medical therapy	Healthy subjects	Kruskal–Wallis ANOVA *p* value
Patients	23	42	69	
Quality of life	8 (4–10)	9 (3–10)	8 (4–10)	0.102
Quality of health	7 (3–10)	8 (3–10)	8 (6–10)	0.027
Energy level	8 (3–10)	8 (3–10)	8 (4–10)	0.493
CGQL	7.6 (12–30)	8.3 (3–10)	8.0 (5–10)	0.236

Table 5 Patient Characteristics and Long-Term Outcome of Hinchey Stage 1 DD

	Colonic resection	Medical therapy	*p* value
Admission			
Patients	9	17	
Gender (male)	3 (33%)	8 (47%)	0.682
Age at admission	65 (42–72)	71 (32–84)	0.418
Previous attack of DD	9 (100%)	3 (18%)	0.001
Symptoms			
Fever	1 (11%)	6 (35%)	0.357
Abdominal pain	6 (66%)	15 (88%)	0.302
Stipsis	3 (33%)	7 (41%)	1.000
Diarrhea	0 (0.%)	5 (29%)	0.128
Rectal bleeding	1 (11%)	2 (12%)	1.000
Bloating	3 (33%)	6 (35%)	1.000
Follow-up			
Readmission (patients)	4 (44%)	3 (18%)	0.181
Symptoms			
Fever	1 (11%)	2 (12%)	1.000
Abdominal pain	5 (55%)	7 (41%)	0.683
Stipsis	5 (55%)	7 (41%)	0.683
Diarrhea	0 (0%)	3 (18%)	0.529
Rectal bleeding	0 (0%)	1 (6%)	1.000
Bloating	2 (22%)	7 (41%)	0.417
Quality of life			
Quality of life	8 (4–10)	9 (3–10)	0.575
Quality of health	7.5 (3–10)	8 (3–10)	0.373
Energy level	7.5 (5–10)	8 (3–10)	0.893
CGQL	24 (12–30)	24 (9–30)	0.948

Although two of our patients treated with medical therapy later required surgery, none undergoing colonic resection needed any further resection, and the rate and timing of surgical procedures was not significantly different in the two groups. Even if this result could be due to the small sample size of the groups studied, it nonetheless reflects the seemingly low risk of surgery in these patients. Paradoxically, patients with a simple sigmoidectomy had a lower cumulative re-admission rate than those who had left hemicolectomy, suggesting that resection is probably efficacious because the sigmoid high pressure zone is ablated and not because the large bowel affected by the DD has been removed.

Quality of life scores obtained in the two groups of patients and in healthy subjects were similar as were the responses to the current quality of life and current energy level. There was, likewise, no significant difference in the Hinchey stage 1 patients with regards to the CGQL total score or response to the single questions. These data seem to reflect the similarity of symptom rates at follow-up between the patients treated with colonic resection and those who received medical therapy. In fact, at follow-up, the frequency of abdominal pain, constipation, diarrhea, rectal bleeding, and bloating were similar in the two groups.

Nevertheless, quality of life of these patients was not different from that of healthy subjects, and it is known that DD negatively affects quality of life,[24] so an improvement of sorts might be hypothesized. It has also been reported that cyclic treatment with antibiotics or anti-inflammatory drugs relieves symptoms and improves HRQL in patients with DD.[24] The effect of surgery on quality of life could indeed be equivalent, and the low discriminative ability of generic quality of life questionnaires in general and the CGQL in particular may have influenced the results being reported.[19] This questionnaire was chosen for this study because it is easy to use during a telephone interview that could be more affordable for elderly patients than coming to the clinic for a face-to-face interview or self administration of a mailed questionnaire.

Post-operative complications are, in any case, an important consideration, and in effect, current quality of health was significantly worse in the patients who had undergone colonic resection. Constantides et al. had already reported that there is a significant impact on the physical health of elderly subjects and postoperative complications following this procedure.[25] The risks related to colostomy should in any case be considered carefully as patients who have undergone this procedure for benign processes have found it difficult to adapt to their new body situation and have reported a worse quality of life.[26]

The main limit of this observational study is the low number of patients who had surgery for DD at the Hinchey stage 1, and the small sample size of this crucial group might make our findings less conclusive. Therefore, further larger studies with a longer follow-up and more detailed quality of life questionnaires are advisable to investigate the actual impact of surgery on quality of life of these patients.

In conclusion, our results indicate that there are no long-term advantages to colonic resection for DD, and these data seemed to be supported by the analysis of the small group of Hinchey stage 1 patients. Thus, in our opinion, surgical resection should be reserved for patients who present with a complicated DD and not for patients who present a mere abdominal discomfort attributed to DD.

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Small Intestinal Submucosa as a Bioscaffold for Tissue Regeneration in Defects of the Colonic Wall

Jens Hoeppner · Vladan Crnogorac · Goran Marjanovic · Eva Jüttner · Wojciech Karcz · Hans-Fred Weiser · Ullrich Theodor Hopt

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Abstract
Background Small intestinal submucosa (SIS) has proved considerable regenerative capacity for repair of bowel wall defects at different locations. This study assesses the effectiveness of SIS in the repair of defects at a gastrointestinal location with strong bacterial contamination.
Methods Fourteen domestic pigs had a 4.5×1.5 cm full-thickness defect created on the wall of the descending colon. Repair was done by suturing an SIS patch to the defect. Grafts were harvested after 30, 60, and 90 days. Outcomes were evaluated on the basis of animal survival, clinical course, and macroscopic, histological, and immunohistochemical assessment.
Results All animals survived the scheduled observation period. No patch failure and no postoperative leakage occurred. No luminal narrowing occurred at SIS-patched colon. Morphometric examination revealed contraction of the patched area of 77% after 30 days and more than 90% after 60 and 90 days. By 60 and 90 days, all animals showed mucosal regeneration at the margins of the graft. By 90 days, regeneration of smooth muscle cells was present at the original site of the muscularis mucosae. None of the reconstructed areas showed complete mucosal coverage or regeneration of a structured muscular layer.
Conclusion SIS can be used effectively for patch repair of colonic defects in a porcine model. Distinctive contraction of the reconstructed area and limited architectural regeneration of the bowel wall suggest limitation of morphologic regenerative capacities in large-bowel regeneration.

Keywords Extracellular matrix · Small intestinal submucosa · Tissue engineering

J. Hoeppner · G. Marjanovic · W. Karcz · U. T. Hopt
Department of General and Visceral Surgery,
University of Freiburg,
Freiburg, Germany

E. Jüttner
Department of Pathology, University of Freiburg,
Freiburg, Germany

V. Crnogorac · H.-F. Weiser
Department of Surgery, Diakoniekrankenhaus Rotenburg,
Rotenburg, Germany

J. Hoeppner (✉)
Department of General and Visceral Surgery,
Albert-Ludwigs-University Freiburg,
Hugstettter Str. 55,
79106 Freiburg, Germany
e-mail: jens.hoeppner@uniklinik-freiburg.de

Introduction

Technical progress in the field of tissue engineering and regenerative medicine has led to new possibilities for the repair of gastrointestinal defects and for gastrointestinal tissue regeneration. A promising approach for the repair of gastrointestinal defects is the substitution of the bowel wall with extracellular matrices. Extracellular matrices are acellular, collagenous resorbable scaffolds of biological origin. The best-established material is "small intestinal submucosa" (SIS). SIS is a biodegradable, commercially available, acellular, immunologic inert collagen matrix, which is extracted from the submucosal layer of porcine small bowel. SIS remains biologically inert graft material without provoking immune-mediated inflammatory reactions.[1] In recent years, experimental studies showed considerable success for the use of SIS as a tissue graft in blood vessels, bladder, ureter and tendon.[2–5] Different experimental studies have been carried out to evaluate SIS in substitution and

remodeling of gastrointestinal defects. Biliary duct, small bowel, stomach, and esophagus have been investigated. It has been shown that SIS promotes the regeneration of native gastrointestinal tissue with normal architecture consisting of mucosa, muscularis, and serosa.[6–9] The first experimental work of successful cecal-defect repair with SIS in a rodent model was recently published.[10] The aim of our study was to evaluate SIS as a scaffold for gastrointestinal tissue regeneration at the descending colon. We studied the feasibility of SIS for substitution of a large full-thickness tissue defect of the descending colon in a pig model.

Materials and Methods

Animals and Anesthesia

Fourteen female German domestic pigs with a median weight of 33.2 kg (range 30.5–41.3 kg) were used for this investigation. The study was approved by the Animal Care and Use Committees at the University of Veterinary Medicine Hannover and local district government of Lower Saxony in Germany. All procedures in this study were performed under strict adherence to the German Animal Welfare Law and meet the standards set in the "Guide for care and use of laboratory animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985). The pigs were weighed before surgical procedure and at regular intervals during postoperative observation. The animals were fed with a standard diet and water ad libitum. For reduction of colonic fecal load, bowel preparation was begun with a preoperative fluid diet orally 48 h before operation. All surgical procedures were performed under general anesthesia. Premedication was done with intramuscular application of azaperon (2 mg/kg), ketamine hydrochloride (15 mg/kg), and atropine (0.05 mg/kg). Anesthesia was deepened with intravenous application of atracriumbesalat and hypnomidate (10 mg/kg). Subsequently the animals were intubated and artificially ventilated with isoflurane and a mixture of oxygen and dinitrogen oxide.

Surgical Technique of Colonic Defect Repair

The abdomen was shaved and prepared with iodophor. A midline incision was performed under sterile conditions. After exposure of the peritoneal cavity, the descending colon and rectum were identified and gently exposed. A 4.5×1.5 cm antimesenteric elliptical full-thickness defect of the anterior wall of the descending colon was created by electrosurgical excision. An elliptical template was used in order to keep the defect a consistent size in all animals. A swab was taken from open colon, the sample was incubated, and bacterial colonic microflora determined. Remaining fecal contents, which were present in all animals, were removed by iodine gauze. The repair of the defect was done by implantation of a 5×2 cm four-layer SIS Patch (Surgisis; Cook Surgical, Lafayette, IN, USA). In accordance with the manufacturer's recommendation, the SIS patches were allowed to rehydrate by immersion for 10 min in sterile Ringer's solution before use. The fixation of the SIS patch was done with absorbable polyglycolic acid 3/0 single knot suture. Stitches were placed at a distance of 2 mm to the edge of the SIS patch which overlapped the serosa for this distance. The initial size of the SIS-patched area measured from the luminal side was 5.78 cm^2. Four single non-resorbable Prolene 4/0 sutures were placed at the margins of the SIS Patch as markers for later identification of the patch. After physiological re-arrangement of the abdominal organs, the abdominal cavity was closed in layers with absorbable sutures.

Postoperative Management

In the postoperative period, the pigs were examined daily by a veterinarian for signs of wound infection, fever, abdominal pain, behavior, bowel movements, stool, and eating behavior.

Groups and Procedure of Scheduled Relaparotomy

The animals were randomly divided into three groups. In ten animals, short-term follow-up was done for 30 days (group A). Two animals were observed for 60 days (group B), and two pigs survived 90 days for long-term observation (group C). Thirty, 60, or 90 days after surgical intervention, depending on the study group to which the animals were assigned, they were reanesthetized, and relaparotomy was performed. The peritoneal cavity was examined for signs of impaired colonic healing, e.g., peritonitis, intra-abdominal abscess, or fibrinous coverings. The integrity of the patch repair site was inspected and checked for signs of wound dehiscence, pericolic abscess formation, necrosis, fistulas, adhesions, and strictures. The descending colon and adherent organs were removed en bloc for detailed macroscopic and microscopic evaluation, and the pigs were killed.

Macroscopic and Microscopic Examination

During ex situ preparation, the specimen was always kept moist with 0.9% saline. The diameter of the colonic lumen at the site of the SIS patch was measured and compared to the diameter of the colonic segments lying proximal and distal to the reconstructed area at descending colon. Then the descending colon was cut longitudinally along the mesenteric border. First, the serosal site was checked. Condition and location of the SIS-patched area, macro-

scopic vascularization of the patch, and existence of bowel necrosis or fistulas were assessed. The specimen was turned around and the mucosal surface examined. Digital photographs were taken. Morphometric examination was carried out with PC Software "ImageJ" (National Institutes of Health, Bethesda, MA, USA). For histological examination, 2-mm-wide strips were cut from the site of SIS-Patch repair. The strips were fixed in phosphate-buffered 4% formaldehyde for 4 days and subsequently embedded in paraffin. The sections were cut in 5 μm slides and stained with hematoxylin and eosin. Furthermore, Elastica van Gieson stain was done for differentiation between smooth muscle and collagen fibers.

Immunohistochemical Examination

An immunohistological stain for alpha smooth muscle actin (DAKO, clone 1A4) was used for analysis of muscular regeneration. The protocol followed routine diagnostic staining procedures, and staining was performed by an autostainer, ensuring reproducibility (DAKO Autostain Plus Link).

Statistical Analysis

All data are expressed as the mean ± standard error of the mean.

Results

Colonic Microflora

Bacteroides spp., *Lactobacillus* spp., *Escherichia coli*, *Streptococcus bovis*, *Streptococcus fecalis*, and *Streptococcus feacium* were isolated in all animals in colonic bacteriology at the time of operation.

Survival and Clinical Examination

All animals in the study groups survived for the scheduled postoperative periods. All animals tolerated their oral intake without evidence of intestinal obstruction or dysfunction and gained weight significantly (group A: preop 31.9±0.87 kg, 30 days postop 40.2±0.98 kg; group B: preop 33.4±0.10 kg, 60 days postop 53.4±1.15 kg; group C: preop 39.7±1.6 kg, 90 days postop 71.4±4.7 kg). None of the animals showed clinical signs of illness due to colonic leakage or intra-abdominal infection.

Macroscopic Examination

Five animals developed superficial wound infections without signs of systemic infection and without impairment of further clinical course. Macroscopic examination of the abdominal cavity at the end of the experiment showed no leaks, no fistulas, no stenosis, and no necrosis of the bowel wall at the site of colonic patch repair. No manifestation of intra-abdominal infection, intra-abdominal abscess, or localized or generalized peritonitis could be detected. Macroscopic detection of the patches from the serosal view was difficult in all groups due to complete or partial coverage of the patched area with adhesions. There were no remarkable differences in colonic diameter between the SIS-patched segment and the colonic segments lying proximal and distal to the reconstructed segment. The exact boundary of the SIS-patched area could not be identified from the serosal view in any of the animals. Reliable identification of the patched area could be archived by identification of the four non-resorbable Prolene sutures which were placed surrounding the SIS-Patch. If not covered by adhesions, the serosal side of the patched area was seen to be covered by healed scar after 30, 60, and 90 days. Adhesions were frequently observed in all groups. Adhesive organs were, in descending frequency, uterus horns, ovaries, bowel segments, and bladder.

Morphometric Examination

The lumen side of the patched area in all groups was identified as an ulcer (Fig. 1). The size of this central ulcer ranged from 0.854 to 1.799 cm^2 after 30 days, from 0.094 to 0.480 cm^2 after 60 days, and from 0.339 to 0.561 cm^2 after 90 days. The stitching holes from the fixation of the SIS patch were recognizable at the margins of the ulcer, indicating contraction of the patched area. At 30 days, the patched area contracted in mean to 23% of initial size. The area contracted in mean to 5% of the initial size at 60 days and 8% at 90 days (Table 1).

Microscopic Examination

The SIS graft was not detectable in any of the animals in any group. At 30 days, the defects were filled by granulation tissue with noticeable neovascularization. Infiltration by inflammatory cells and foreign body reactions surrounding the suture material were noted. Minimal regeneration of the mucosal layer at the margins of the defect was detectable in half of the animals (Table 1). The other layers of the bowel wall were replaced by granulation tissue in all animals (Fig. 2). Regeneration of the mucosal layer at the margins of the defect was detectable in both animals examined after 60 days. The other layers of the bowel wall were completely replaced by granulation tissue and fibrosis. Infiltration by inflammatory cells and foreign body reactions surrounding the suture material were decreasing. Regeneration of the mucosal layer at the

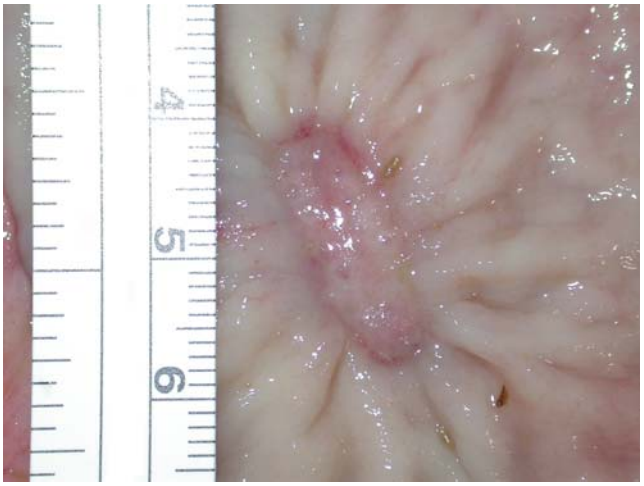

Figure 1 Macroscopic aspect of the mucosal surface 30 days after SIS grafting. Central ulcer measuring 1.8×0.6 cm^2 at SIS-grafted area of the colonic wall.

margins of the defect was detectable in both animals examined at 90 days. In the center of the patched area was an ulcer without complete epithelial covering. Infiltration by inflammatory cells was decreasing. Architecturally, the submucosal, muscular and serosal layers were not organized. Thin strands of smooth muscle cells could be detected at the margin of the ulcer at a level corresponding to the muscularis mucosae of the undisturbed colonic wall (Fig. 2).

Immunohistochemical Examination

Staining for alpha-smooth muscle actin did not show any regeneration of structured muscular layers after 30 and 60 days. After 90 days (Fig. 3), immunohistochemical examination showed that the SIS-regenerated bowel wall had an alpha-smooth muscle actin-positive layer located in the inner portion of the intestinal wall extending to the area formerly occupied by the muscularis mucosae (Fig. 4). The portions natively taken by the muscularis propria were filled by fibrosis (Fig. 3).

Discussion

SIS is a commercially available, acellular collagen matrix derived from porcine jejunum which provides a biological scaffold for tissue regeneration. It has been shown that SIS provokes a host response for neoangiogenesis, tissue regeneration, and restoration of structure and function that is specific to the implantation site.[11] The mechanisms for this response of site-specific repair are not known. The presence of different proteins responsible for cellular migration and attachment, like fibronectin and heparin sulfate proteoglycan, and different growth factors, like fibroblast growth factor, vascular endothelial growth factor, and transforming growth factor-β, which have been identified in SIS, could be one reason for this phenomenon.[11–13]

Table 1 Study Groups, Scheduled Survival, Shrinkage of SIS Reconstructed Area, Microscopic and Immunohistochemical Examination for Structured Regeneration of the Colonic Wall at Grafted Area

Sequential No.	Survival (d)	Residual mucosal defect at scheduled date (cm2)	Regeneration of Bowel wall layers (microscopic and immunhistochemical examination)
		mean*	
Group A		1,33 (23%)	
1	30	1.19	No mucosal regeneration, no muscular regeneration
2	30	1.63	Incomplete marginal mucosal regeneration, no muscular regeneration
3	30	1.79	No mucosal regeneration, no muscular regeneration
4	30	1.01	No mucosal regeneration, no muscular regeneration
5	30	1.62	Incomplete marginal mucosal regeneration, no muscular regeneration
6	30	1	Incomplete marginal mucosal regeneration, no muscular regeneration
7	30	1.14	No mucosal regeneration, no muscular regeneration
8	30	1.79	Incomplete marginal mucosal regeneration, no muscular regeneration
9	30	1.33	No mucosal regeneration, no muscular regeneration
10	30	0.85	Incomplete marginal mucosal regeneration, no muscular regeneration
Group B		0,28 (5%)	
1	60	0.48	Incomplete marginal mucosal regeneration, no muscular regeneration
2	60	0.09	Incomplete marginal mucosal regeneration, no muscular regeneration
Group C		0,45 (8%)	
1	90	0.56	Incomplete marginal mucosal regeneration, muscular regeneration at muscularis mucosae
2	90	0.33	Incomplete marginal mucosal regeneration, muscular regeneration at muscularis mucosae

*Initial size of SIS graft measured from mucosa side was 5,78 cm2. Comparison to initial size of SIS graft in % is enclosed in brackets.

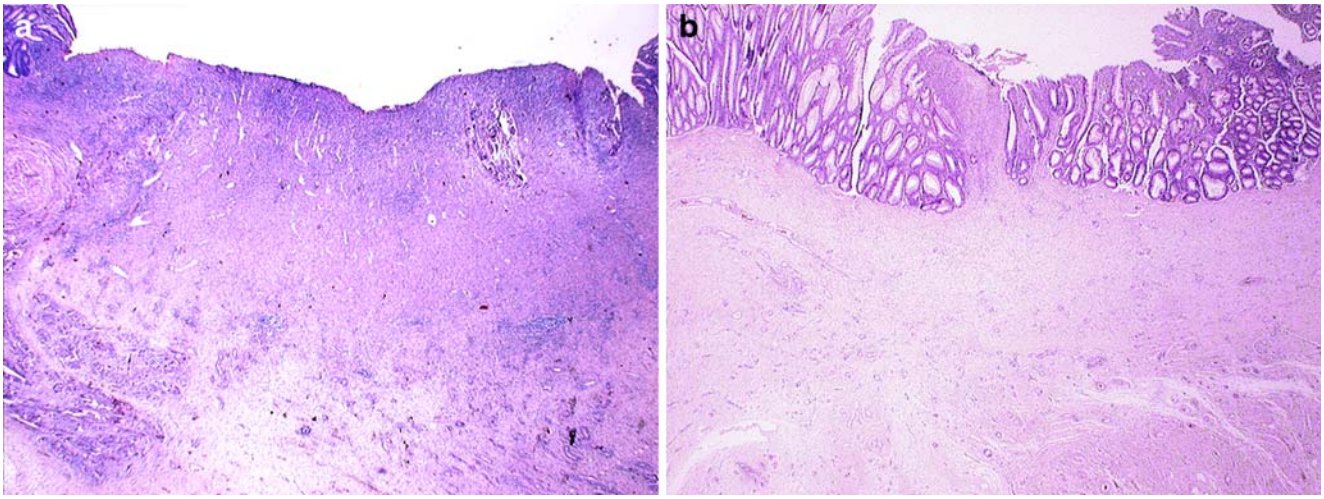

Figure 2 Microscopic view of the grafted area (hematoxylin and eosin stain; magnification ×100). **a** 30 days. Complete closure of the defect by granulation tissue. The SIS graft is not detectable. All layers of the colonic wall are replaced by granulation tissue and early fibrosis. Early neovascularization is present. Foreign body giant cell reaction is detectable in the area of suturing. **b** 90 days. Wide regeneration of the mucosal layer at the margins of the defect. Persisting ulcer without mucosal covering in the center of the defect. Submucosa and muscularis propria are replaced by mainly vascularized fibrous tissue. The SIS graft is not detectable.

Several experimental studies showed success for the use of SIS as a tissue graft in blood vessels, bladder, ureter, and tendon.[2–5] Different experimental studies have been done which proved the potency of small intestinal submucosa as a bowel wall substitute for repair of bowel wall defects at different gastrointestinal locations. Considerable regenerative capacity could be shown in esophagus, stomach, bilary duct, and small bowel.[6–9,14]

Regeneration of small intestine with SIS as a bioscaffold was first examined in a canine model. Two months after small bowel defect patch repair with SIS, an organized mucosal layer was present at the SIS-reconstructed area. After 3 months, the complete absence of SIS was described. Fifty percent contraction of the SIS-patched area was noted by 4 months. At 6 months, only minimal architectural differences between native and regenerated small bowel could be shown; histological examination demonstrated the presence of mucosa, submucosa, smooth muscle layer, and serosa.[7] Another study demonstrated the successful use of SIS for patch repair of large jejunal defects in rabbits. After

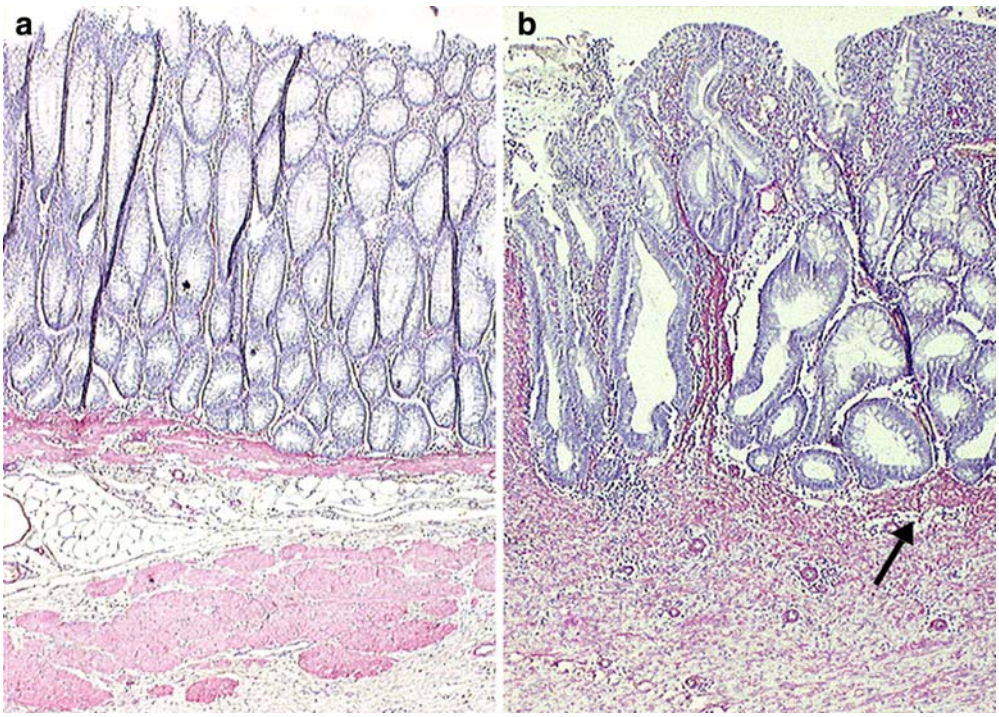

Figure 3 Immunohistochemical staining for alpha-smooth muscle actin (magnification ×250). Smooth muscle cells are marked *red*. **a** Normal porcine colon. **b** SIS-regenerated porcine colon by 90 days. Regeneration of the mucosal layer including presence of smooth muscle cells (marked by *arrow*) at the area formerly occupied by the muscularis mucosae was detectable. Beginning fibromuscular organization of the deeper layers, but no anatomical muscularis propria could be shown.

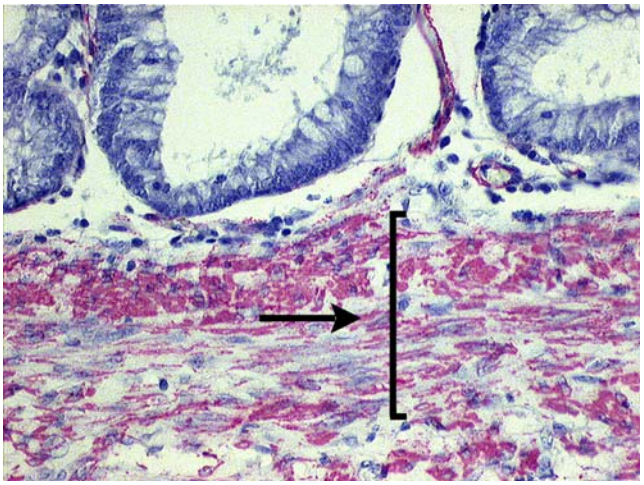

Figure 4 Immunohistochemical staining for alpha-smooth muscle actin (magnification ×2,000). Regeneration of a strand of smooth muscle cells at the original site of the muscularis mucosae.

4 weeks of regeneration, the grafts showed that the remodeled bowel wall contained a mucosal columnar epithelial layer, and the graft was infiltrated by blood vessels, fibroblasts, and mononuclear cells. By 6 weeks, the lumen of SIS completely regenerated to a small intestinal mucosa with villus-like configuration. Shrinkage of the SIS-patched area of 25% to 50% was reported.[14]

The repair of esophageal defects with patches of SIS was examined in a canine model. After 35 days, only remnants of SIS were identified at the implantation site. After 50 days, no patch material could be identified. Replacement of SIS by skeletal muscle, which was oriented appropriately and contiguous with adjacent normal esophageal skeletal muscle, organized collagenous connective tissue, and a complete and intact squamous epithelium, have been reported.[9]

Most experimental studies have been performed in sterile environments or at locations of little or moderate bacterial contamination. Only single observations have been reported under conditions of gross bacterial or fecal contamination. The use of SIS for patch angioplasty of the iliac artery in the presence of intra-abdominal stool contamination due to colonic perforation was recently examined. After 4 weeks, the SIS patches showed complete incorporation and significantly less infection compared to polytetrafluoroethylene-patch angioplasty. The SIS-reconstructed areas appeared to be nearly indistinguishable from native vessel.[15] In the field of surgery of the body wall, SIS was examined clinically in repair of infected ventral and inguinal hernias. Failure of treatment with early recurrent hernia was observed in seven of 20 cases.[16] The use of SIS for the repair of large bowel perforations in a rodent model was recently evaluated for the first time. Full-thickness cecal defects were repaired by SIS patches. No leakage occurred, no shrinkage of the patched area was reported, and after 6 months, the defect was reported to be completely replaced by bowel wall of normal architecture. However, the loss of the SIS patch into the cecal lumen was reported in few animals. The authors of this study proposed SIS as a method to promote healing and protect large bowel anastomoses from leakage.[9]

Transfer of these findings to a large animal model was mandatory for further evaluation of SIS in promoting healing and regeneration of the colonic bowel wall and before any human use of SIS for indications of colonic defect repair or protection of colonic anastomoses. On the one hand, SIS is a promising approach as anastomotic sealing for the protection of high-risk colonic anastomoses. On the other hand, it appears to be applicable for the repair of anastomotic fistulas, e.g., recto-vaginal fistulas or entero-cutaneus fistulas after anastomotic dehiscence. In our study, SIS was used as an allograft in a porcine model. Although in general anastomotic defects are only of small diameter, the creation of 4.5×1.5 cm defects in our experimental model was chosen in order to study the contraction of the grafted area and to reliably assess the quantity and quality of colonic tissue regeneration. It is the first study to evaluate the feasibility of repairing a large full-thickness colonic defect using SIS in a large animal model. It showed that SIS was effective in the repair of large tissue defects at a gastrointestinal location in the presence of gross bacterial contamination.

No remaining SIS material could be detected 30 to 90 days after implantation in the colonic wall. Since SIS is reported to be extensively degraded within 28 to 60 days at gastrointestinal, urinary, and vascular implantation sites, it is likely that nearly complete degradation of the patch material occurred.[9,15,17] The ultimate fate of the SIS in our study remains unclear, whether it was completely biologically degraded or partially degraded and lost into the colonic lumen.

The architectural regeneration of the bowel wall layers at the area reconstructed with SIS was less distinctive than reported at other gastrointestinal locations. After a follow-up of 3 months in contrast to reports mentioned above, complete mucosal coverage of the defect was not detectable in any of the animals in our study. Furthermore, no significant regeneration of the muscularis propria was present in any of the animals. Similar to our findings, incomplete mucosal coverage and missing muscular regeneration have been reported in the repair of duodenal defects with SIS.[18,19] The extent of contraction of the area repaired with SIS in our study was higher than described for patch repair at other gastrointestinal locations.[7,10,14] A possible reason for this difference may be extended scarred healing and less SIS-induced structured architectural regeneration due to faster structural and biochemical degradation of SIS in the presence

of large bowel microflora. The similarity to the findings in duodenal patch repair with SIS could be explained by likewise early degradation of the SIS in the presence of high concentrations of pancreatic enzyme and bile.

Tissue regeneration, angiogenesis, connective and epithelial tissue growth, and tissue differentiation induced by SIS are supposed to be mediated by different regulatory proteins like fibronectin, heparin sulphate proteoglycan, FGF-2, TGF-β, and VEGF.[11–13] In addition, the three-dimensional architectural structure of the fibrillar collagens and adhesive glycoproteins in the naturally occurring biopolymer SIS may be a factor for structured tissue regeneration induced by SIS.[11] The differences in SIS-induced tissue regeneration at various gastrointestinal locations could be explained by the effects of different chemical and bacteriological environments on the integrity of the collagenous matrix and the content and intactness of the regulatory and adhesive proteins.

In summary, the results of this study suggest that large defects of the porcine bowel wall at lower colonic site can be successfully repaired by patch repair with SIS grafts. It implies that SIS may be evaluated for operative therapy of colonic fistulas, colonic injuries, or for prevention of anastomotic leakage by surgical reinforcement of colonic anastomosis. Distinctive contraction of the reconstructed area and limited architectural regeneration of the bowel wall suggest some limitation of regenerative capacities of SIS in large-bowel regeneration. Whether gross bacterial contamination at the implantation site or other site-specific factors are the reason for these findings has to be determined in further experimental work.

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Does Mesorectal Preservation Protect the Ileoanal Anastomosis after Restorative Proctocolectomy?

Andreas D. Rink · Irina Radinski · Karl-Heinz Vestweber

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Abstract
Background and aims The technique of rectal dissection during restorative proctocolectomy might influence the rate of septic complications. The aim of this study was to analyze the morbidity of restorative proctocolectomy in a consecutive series of patients who had rectal dissection with complete preservation of the mesorectum.
Patients and methods One hundred thirty-one patients who had restorative proctocolectomy for chronic inflammatory bowel disease with handsewn ileopouch-anal anastomosis (IPAA) and preservation of the mesorectal tissue were analyzed by chart reviews and a follow-up investigation at a median of 85 (14–169) months after surgery.
Results Only one of 131 patients had a leak from the IPAA, and one patient had a pelvic abscess without evidence of leakage, resulting in 1.5% local septic complications. All other complications including the pouch failure rate (7.6%) and the incidence of both fistula (6.4%) and pouchitis (47.9%) were comparable to the data from the literature.
Conclusion The low incidence of local septic complications in this series might at least in part result from the preservation of the mesorectum. As most studies do not specify the technique of rectal dissection, this theory cannot be verified by an analysis of the literature and needs further approval by a randomized trial.

Keywords Handsewn anastomosis · Ileoanal anastomosis · Pouch · Local septic complications · Rectal dissection

Introduction

Restorative proctocolectomy is the treatment of choice for the surgical management of ulcerative colitis for most patients, as the large bowel is completely removed and anal continence is maintained with an acceptable stool frequency and anal function.[1–4] Performing the procedure without morbidity, especially preventing local septic complications, is a major determinant of the long-term success, as local septic complications impair the functional outcome and increase the risk of consecutive pouch failure.[5–8]

While a double-loop J-pouch is the generally accepted ileal reservoir, further technical features are still under debate including the way the ileopouch-anal anastomosis (IPAA) is fashioned[9] and the question whether a protective ileostomy should be used routinely or selectively.[10–12]

One technical detail that might also influence perioperative morbidity is the technique of rectal dissection. Most surgeons prefer to mobilize the rectum in the avascular mesorectal space, as this allows bloodless preparation in a clearly defined anatomical plane and because they are used to this technique from rectal cancer surgery. However, the mesorectal fat is completely removed leaving behind a large cavity at the pelvic floor, which may be filled with hematoma and increase the risk of pelvic abscess formation later. Furthermore, this technique may increase the risk of damaging the pelvic nerves with the consequence of bladder or sexual dysfunction. If the rectal dissection is performed close to the bowel wall, the

A. D. Rink · I. Radinski · K.-H. Vestweber
Deparment of Surgery, Leverkusen General Hospital,
Am Gesundheitspark 11,
51375 Leverkusen, Germany

A. D. Rink (✉)
Clinic of General and Abdominal Surgery,
Johannes Gutenberg-University,
Langenbeckstr. 1,
55101 Mainz, Germany
e-mail: andreas.rink@ukmainz.de

mesorectal fat can be completely preserved. Most of the aboral part of the pouch is surrounded by a funnel-like mesorectal wrap, no cavity remains at the pelvic floor, and the mesorectum covers at least the linear suture lines of the IPAA that might reduce the risk of local septic complications. Notably, some studies have reported increasing rates of anastomotic leakage after introducing total mesorectal excision as a new standard for the treatment of rectal cancer.[13,14] In formerly performed conventional rectal cancer surgery, the mesorectum had often been removed incompletely, resulting in higher local recurrence rates[15] but obviously in less anastomotic leakage, as well.[13,14]

To evaluate the hypothesis of a protective effect of the preserved mesorectum, we analyzed the morbidity of restorative proctocolectomy for the treatment of ulcerative colitis and indeterminate colitis in a consecutive series of patients treated over a period of 12 years at our institution with this technique.

Patients and Methods

All patients having had a restorative proctocolectomy between January 1990 and December 2002 at our institution were identified by a chart review. We included all patients with handsewn IPAA in which the rectal preparation was performed close to the bowel so that the mesorectal fat was preserved. Therefore, we did not include patients who had been treated for ulcerative colitis associated with low rectal cancer, as total mesorectal excision was performed in these cases. We further excluded all patients with Union Internationale Contre le Cancer stages II and III colorectal cancer and other advanced malignancies. To make the data as consistent as possible, we did also not include patients that were treated with restorative proctocolectomy for other indications, as for example familial adenomatous polyposis (FAP).

Surgical Technique

Colectomy was performed by dissecting the mesentery close to the bowel wall, as far as dysplasia or cancer had been excluded by preoperative colonoscopy. Especially, the ileocolic artery was thoroughly preserved. Rectal preparation was performed close to the bowel wall in all cases so that the mesorectal fat was preserved. All IPAA procedures were performed by the first (ADR) or the senior author (KHV). The ileum pouch was designed as a 15- to 20-cm J-shaped reservoir, using linear staplers (two 90-mm cartridges and, optionally, an additional 50-mm cartridge) inserted from the oral side, leaving behind a small bridge of undissected bowel wall close to the apex. Mucosectomy was performed transanally in all cases. A 2- to 3-cm muscular cuff was preserved. The ileopouch-anal anastomosis was performed by placing four to eight anchoring sutures (polyglactin, Vicryl® 3–0, Ethicon) to the top of the muscular cuff to fix the pouch wall approximately 2 cm above the apex to the top of the muscular cuff. Then, the apex was incised, and the actual IPAA was fashioned with 12–18 polyglactin 3–0 stitches (Vicryl®, Ethicon) suturing the whole bowel wall to the anoderm. The pouch was drained using a 24 Ch urinary catheter inserted through the anus for 5–7 days.

A protective ileostomy was performed routinely, if the IPAA was not completely free of tension or if dissection of ileal branches or the periphery of the central route of the superior mesenteric artery necessary to achieve a sufficient length of the bowel caused an apparent reduction in blood flow at the apex of the pouch. Furthermore, diversion was also used routinely in all patients on immunosuppressive drugs or on cortisol in a dose of 20 mg or higher. If patients who did not meet at least one of these criteria asked for a one-stage procedure, an ileostomy was abandoned. A suprapubic catheter was routinely installed into the bladder. It was removed postoperatively if the patients were well mobilized and bladder evacuation was proven to be sufficient (residual urinary volume less than 50 ml). Closure of ileostomy was intended 12 weeks after initial surgery. Before ileostomy closure, the integrity of the IPAA was evaluated by clinical investigation, contrast enema, and endoscopic examination.

Follow-Up

Between January 2003 and August 2004, all patients were invited for a personal interview and a follow-up investigation. Those patients who agreed to take part in the follow-up but who where not able to come for a personal interview and an examination had a telephone interview. Data on the long-term course of those patients who were not available for an interview were collected from the hospital charts, as well as by contacting the patient's gastroenterologists and primary care physicians. However, data on pouchitis and fistulas were only analyzed from those patients who had a personal or a telephone interview, because data collection without asking the patients specifically for the symptoms might underestimate the real incidence of theses criteria. For functional evaluation, these patients were also asked to document the frequency of defecation as well as their bowel habits in a 14-day incontinence diary. Incontinence was measured using an incontinence score according to Vaizey.[16]

Morbidity Analysis

The data were analyzed for both early morbidity (complications presenting up to 3 months after initial surgery) and late morbidity (complications presenting later than 3 months after surgery). Anal fistulas, presenting within the first 3 months after IPAA, were classified as anastomotic leakage and, therefore, as early local septic complications.

Results

Restorative proctocolectomy with handsewn IPAA was performed in a consecutive series of 142 patients with chronic inflammatory bowel disease between January 1990 and December 2002 at our institution. However, 11 patients were excluded for colorectal cancer (n=10) or for an advanced primitive neuroectodermal tumor of the rectosigmoid junction. One hundred twenty-three of the remaining 131 patients had the diagnosis of ulcerative colitis. Eight patients with the likely diagnosis of ulcerative colitis (UC) also had some evidence of Crohn's disease and were classified as indeterminate colitis. Of the 131 patients, 73 were male. The median age of the patients was 33.0 (12–70) years at the time of restorative proctocolectomy and 25 (5–59) years at the onset of the bowel disease, respectively. The median duration of the disease at the time of surgery was 94 (2–325) months.

Data on early morbidity were available from all 131 patients. Four patients were lost in follow-up, and four patients had died. Three of these four patients had their protective ileostomies closed and, therefore, had a functioning pouch before death. Five patients did not have their protective ileostomies closed. Three of these patients were satisfied with the stoma and decided not to have it closed (two men, 71 under 46 years old, one woman, 51 years old), and two had not yet had their stomas closed at the time of follow-up. Thus, data on the long-term success of IPAA were available from 118 patients. Ninety-four of these patients had a personal (n=75) or a telephone (n=19) interview and could therefore be evaluated for pouchitis, fistulas, and the functional outcome.

In 14 of the 131 initially treated patients, the restorative proctocolectomy with IPAA was performed without a protective stoma (one-stage procedure). In another seven patients who had already had prior subtotal colectomy, restorative proctectomy with IPAA had also been performed without an ileostomy, resulting in 21 cases of IPAA performed without a protective stoma. A classical two-stage procedure with restorative proctocolectomy and IPAA as well as a protective ileostomy was performed in 79 cases. Thirty-one patients had a three-stage procedure, with subtotal colectomy and end-ileostomy as a first step, restorative proctocolectomy with IPAA and a protective ileostomy as a second step, and finally the reversal of the ileostomy.

Early Morbidity

Two patients had local septic complications. One female had an anovaginal fistula. The fistula was diagnosed 4 weeks after an IPAA without a protective stoma. The colon was removed 3 months before as an emergency. As the fistula occurred early after the IPAA procedure, it was classified as an anastomotic leakage. It was successfully managed by a transanal approach without protective ileostomy. A second patient had a pelvic abscess that was successfully treated by a computed tomography-guided percutaneous drainage. This patient had the IPAA protected with a diverting ileostomy. However, clinical and radiology examinations did not give any evidence of a stapler-line or anastomotic failure. An infected pelvic hematoma was the most likely cause of this abscess. No further local septic complication occurred. Two other cases presented with peritonitis for other reasons (see Table 1): One patient had urinary peritonitis caused by a dislocation of a suprapubic urinary catheter. The other patient had bacterial peritonitis after restorative proctocolectomy, which had been performed as an emergency procedure for perforated colitis. In this case, a restorative procedure was done instead of a subtotal colectomy and an end ileostomy on the patient's expressive demand. The peritonitis was cured by three programmed re-laparotomies, lavages, and antibiotic treatment. During these procedures, the IPAA and the pouch were investigated by endoscopy and by filling the bowel with dye. Both the stapler-lines of the pouch and the handsewn IPAA were intact. Therefore, the rate of local septic complications was 1.5% (2/131). The rate of anastomotic leakage was 0.8% (1/131) for the total cohort and 4.8% (1/21) for the subgroup of patients treated without a protective ileostomy.

Table 1 summarizes 44 early complications that were documented in a total of 273 procedures. Looking at the 131 IPAA procedures only, 21 complications were documented. None of the patients had bladder dysfunction requiring prolonged urinary diversion. Table 2 presents the cumulative patient-related morbidity separately for the patients treated with one-stage, two-stage, and three-stage procedures, respectively. Notably, cumulative morbidity was highest in the patients treated with the three-stage procedure.

Table 1 Procedure-specific Morbidity

Procedure	Morbidity		Number
Proctocolectomy, IPAA no ileostomy (n=14)	Total		14 (100%)
	No morbidity		10 (71%)
	Morbidity	*Wound hematoma*	1
		Peritonitis[a]	1
		Septicemia[b]	1
		Urinary tract infection	1
Proctocolectomy, IPAA, protective ileostomy (n=79)	Total		79 (100%)
	No morbidity		67 (85%)
	Morbidity	*Intra-abdominal hemorrhage*	1
		Intraluminal hemorrhage	1
		Subileus/ileus	2
		Wound healing disorder	1
		Peritonitis[c]	1
		Catheter sepsis	1
		Pancreatitis	1
		Thrombembolic	1
		Pneumonia	1
		Parastomal fistula	1
		Pelvic abscess	1
Subtotal colectomy, end ileostomy (n=38)	Total		38 (100%)
	No morbidity		25 (66%)
	Morbidity	Wound healing disorder	5
		Pancreatitis	3
		Thrombembolic	1
		Peritonitis[d] (*rectal stump leakage*)	1
		Intraluminal hemorrhage	1
		Catheter sepsis	1
		Urinary tract infection	1
Proctectomy (after initial subtotal colectomy), IPAA, no ileostomy (n=7)	Total		7 (100%)
	No morbidity		6 (86%)
	Morbidity	*Anovaginal fistula*	1 (14%)
Proctectomy (after initial subtotal colectomy), IPAA, protective ileostomy (n=31)	Total		31 (100%)
	No morbidity		27 (87%)
	Morbidity	*Intra-abdominal hemorrhage*	1
		Wound healing disorder	2
		Peripheral nerve paralysis	1
Closure of ileostomy (n=104)	Total		104 (100%)
	No morbidity		94 (90%)
		Anastomotic leakage	1
		Subileus	7
		Disturbed wound healing	2

Complications typed in italics required surgical intervention
[a] Urine peritonitis caused by a dislocated suprapubic urinary catheter
[b] Septicaemia from infected deep vein thrombosis
[c] Peritonitis probably caused from intra-abdominal abscess and insufficient antibiotic treatment during initial surgery
[d] Peritonits caused by leakage of the rectal stump

Late Morbidity

Long-Term Success of IPAA

Nine of 118 patients with long-term success evaluation had had a pouch excision (n=5) or were defunctioned (n=4) at the time of follow-up, resulting in a pouch failure rate of 7.6% (9/118). The reasons for pouch failure were pouch dysfunction in four, severe anal disease in two, and Crohn's disease in three patients. The median follow-up time was 85 (14–169) months.

Fistulas

Six of 94 patients with follow-up interview developed anal fistulas and abscesses more than 3 months after surgery.

Table 2 Cumulative, Patient-related Morbidity

Mode of surgery		Complete procedures	Patients with at least one complication
One-stage	Proctocolectomy with IPAA without protective ileostomy	14	4 (28.6%)
Two-stage	Proctocolectomy with IPAA with protective ileostomy + closure of ileostomy	73	18 (24.7%)
	Subtotal colectomy and end ileostomy + proctectomy with IPAA without protective ileostomy	7	3 (42.9%)
Three-stage	Subtotal colectomy and end ileostomy + Proctectomy with IPAA with protective ileostomy + Closure of ileostomy	31	17 (54.8%)

These complications occurred at a median of 47 (22–131) months after IPAA. Two of the fistulas were cured surgically, one was treated with a permanent seton, and three were managed conservatively.

Pouchitis

Of the 94 eligible patients, 49 (52.1%) never had pouchitis. Of the remaining 45 patients, 17 complained about only one episode of pouchitis, 13 had more than one episode, and 15 had at least one episode of pouchitis per year.

Functional Outcome

The median frequency of defecation at daytime was 6 (range 2–16). The median stool frequency at nighttime was 0.5 (0–5), and the total frequency over 24 h was 7 (2–19). Thirty-five of the 94 patients (36%) used bulky agents on a regular basis, and three patients (3.1%) were not able to postpone defecation for at least 15 min. Fifty patients (53%) were not able to discriminate stool and flatus. Alterations in social life affecting the patients at least sometimes were reported by 20 of 94 individuals (21.3%). The median Vaizey incontinence score was 3 (0–18).

Discussion

Restorative proctocolectomy can be performed with low mortality rates of 0–0.8%.[1,8,17–23] However, the procedure is still associated with a significant morbidity of 19% to more than 50%.[11,18,23–30] To a large extent, this morbidity results from local septic complications of the ileoanal anastomosis. Local septic complications do not only represent a cause of severe, potentially live-threatening secondary complications, but also impair the functional outcome and increase the risk of consecutive pouch failure.[4,7,31,32] The leakage rates of IPAA from various clinical studies are summarized in Table 3. They range between 0% and 12.6% in a series in which patients with FAP were included, exclusively.[33–35] For studies in which only or predominantly patients with inflammatory bowel diseases were included, the leakage rates are somewhat higher, ranging between 2.7% and 15%.[1,7,19,36,37] Other local septic complications are pelvic abscesses without anastomotic leakage, fistulas, and pouch necroses.

Various technical modifications of the pouch procedure have been described, and technical details are still a matter of debate. In contrast to the initially described technique of hand-suturing the apex of the pouch to the anal canal after mucosectomy, the double-stapling technique is increasingly used. In a recent meta-analysis, Lovegrove et al.[9] found that patients with stapled IPAA have better nighttime continence than those with the handsewn alternative, but for other criteria, the functional data were comparable. Another meta-analysis did not show any disadvantage when the handsewn was compared with the stapled technique.[38] Lovegrove et al.[9] found a leak rate of 8.8% for IPAA procedures performed with handsewn anastomosis and 5.2% for stapled procedures, respectively, resulting in an average leak rate of 6.9% (123/1774 patients).

In our series, only one of 131 patients (0.8%) with handsewn anastomosis had leakage of the IPAA, resulting in a total rate of early local septic complications of 1.5%. Fistulas occurred in six of our 94 eligible patients (6.4%). This is within the wide range of 1.6–14.2% of fistulas reported from other trials in which restorative proctocolectomy was predominantly performed for ulcerative colitis.[7,19,26,36,39–41] These fistulas were extremely unlikely to have resulted from silent anastomotic leakage, as none of the fistulas occurred earlier than 22 months after initial surgery. Pouchitis was more likely to have triggered fistula formation. The rate of 47.6% of our patients who had at least one episode of pouchitis and our pouch failure rate of 7.6% are both in accordance with other long-term follow-up studies on IPAA for ulcerative colitis.[8,12,17,21,35,42–45]

The very low rate of local septic complications in our series probably results from various technical aspects: One reason might be the preservation of the mesorectal fat by performing the rectal dissection close to the bowel wall.

Table 3 Leak Rates of the IPAA from Studies on Restorative Proctocolectomy with Respect to the Technique of Anastomosis and Rectal Dissection

Author	Year	Number	Indication UC/IC+CD/FAP/other	Anastomosis handsewn/stapler	Protective ileostomy	Meso rectum	Leakage rate	Percentage
Atkinson[65]	1994	175	158/16/0/0	n. av.	n.av.	n. av.	10/175	5.7
Bauer[18]	1997	392	392/0/0/0	392/0	55.6%	n. av.	35/326	10.7
Björk[33]	2001	59	0/0/59/0	54/5	n.av.	n. av.	0	0
Braun[55]	1995	93	71/0/12/0	0/93	100%	Excised	3/83	3.6
Dayton[36]	2002	644	565/79/0/0	644/0	n.av.	n. av.	18/644	2.7
Everett[56]	1989	60	n. av.	60/0	67.7%	Excised	3/60	5
Fazio[19]	1995	1005	858/75/62/10	n. av.	91.2%	n. av.	29/1005	2.9
Foley[66]	1995	460	382/32/46/0	460/0	99.8%	n. av.	14/392	3.6
Gullberg[67]	2001	86	85/0/1/0	0/86	10.5%	n. av.	7/86	8.1
Heuschen[7]	2002	706	494/0/212/0	706/0	86.5%	n. av.	20/706	2.8
Hultén[68]	1994	307	307/0/0/0	307/0	100%	n. av.	31/307	10.1
Ikeuchi[30]	2004	100	100/0/0/0	100/0	0%	n. av.	4/100	4
Järvinen[54]	1993	200	190/10/0/0	178/22	67%	Preserved	21/200	10.5
Krausz[21]	2005	174	146/0/28/0	94/80	88.4%	n. av.	8/174	4.8
Lake[69]	2004	100	87/4/9/0	9/91	71%	n. av.	5/91	5.5
Mathey[22]	1993	213	164/0/47/0	n. av.	100%	n. av.	11/157	7
Mowschenson[46]	2000	130	127/0/3/0	0/130	21.5%	n. av.	10/130	7.7
McCourtney[57]	1997	103	87/0/9/0	3/100	95.1%	Excised	6/100	6
McIntyre[70]	1997	54	54/0/0/0	27/27	n.av.	n. av.	1/27	7.4
Marcello[26]	1993	460	382/0/0/0	460/0	99.8%	n. av.	14/460	3
MacRae[32]	1997	551	201/25/25/0	322/219	78.8%	n. av.	65/551	11.8
Michelassi[1]	2003	391	378/13/0/0	274/117	65%	n. av.	26/391	6.4
Maartense[58]	2004	60	40/0/20/0	30/30	25%	Excised	4/30	6.7
Panis[59]	1996	93	n. av.	93/0	100%	Excised	3/93	3.2
Pescatori[37]	1988	84	51/0/32/0	84/0	97.6%	Preserved	13/84	15
Pishori[42]	2004	303	285/18/0/0	0/303	97%	n. av.	12/303	4
Poggioli[71]	1993	140	122/0/18/0	74/68	n. av.	n. av.	11/140	7.8
Remzi[34]	2001	119	0/0/119/0	42/77	69%	n. av.	7/119	5.9
Romanos[23]	1997	200	177/13/7/3	53/147	69.5%	n. av.	1/200	0.5
Salemans[53]	1992	72	51/0/21/0	72/0	100%	n. av.	6/71	8.4
Schippers[72]	1998	86	86/0/0/0	0/86	100%	n. av.	4/86	4.7
Sugerman[12]	2000	192	178/6/8/0	n. av.	0%	n. av.	14/192	7.3
Setti-Carraro[73]	1994	110	103/3/0/4	103/3/0/4	94.5%	n. av.	6/110	5.5
Young[29]	1999	100	73/5/20/2	50/50	100%	n. av.	6/100	6
von Roon[35]	2007	189	0/0/189/0	121/54	70.3%	n. av.	22/175	12.6
Ziv[74]	1996	692	692/0/0/0	238/454	92.9%	n. av.	18/692	5.9

n. av.=not available
UC=ulcerative colitis, IC=indeterminate colitis, CD=Crohn's disease, FAP=familial adenomatous polyposis

This results in a small funnel-like cavity in which the pouch sits more tightly in the pelvis than after total mesorectal excision. Although the ileoanal anastomosis itself is not covered by mesorectal fat in most cases, there might be less room in the pelvis for postoperative hematoma or fluid collections carrying a risk of subsequent infection and abscess formation in the deep pelvis. An infected pelvic hematoma might lead to a secondary damage of the IPAA. As presented in Table 3, we also reviewed the literature on IPAA morbidity for a potential impact of the technique of mesorectal dissection. Unfortunately, most authors did not specify the mode of rectal dissection. Only two trials clearly describe a dissection technique close to the bowel wall,[37,54] and five studies describe that the mesorectum was excised.[55–59] The leakage rates seem to be higher in the patients treated with mesorectal preservation. However, these studies had started the patient recruitment in 1980[37] and 1985,[54] respectively, and therefore include, at least to some extent, the learning curve of the procedure and can hardly be compared to more recent data. Apart from that, more than 90% of the patients treated with mesorectal preservation had a handsewn anastomosis, which might be associated with an increased rate of local septic complications.[4,9] Therefore, the hypothesis that the preserved mesorectum protects the IPAA cannot be verified from the published literature.

A second reason for the low rate of local septic complications concerns the anastomotic technique: The two-layered anastomosis we used has the potential advantage of

reducing tension to the actual ileoanal anastomosis. Tension cannot always be avoided by mobilization and preparation of the mesentery, but it may be neutralized by the anchoring stitches placed between the muscular cuff and the pouch. The actual ileoanal anastomosis is basically tension free.

A third reason might be that we used protective ileostomies in most of our patients. One reason was that the majority of the patients were on high-dose steroids or immunosuppressive drugs. In addition, if patients did not specifically ask for a one-stage procedure, we rather performed a protective ileostomy. It is possible that some patients experienced minor leakage that was not recognized under diversion, but this was also true for patients included in other studies on IPAA morbidity (see Table 3). The average leakage rate of all studies in which 100% of the IPAA procedures were done with a diverting ileostomy was 4.9% (64/1296), whereas the average leak rate was 6.2% (18/292) for studies on IPAA without diversion. The latter is in accordance with our 4.8% leak rate in the subgroup of 21 patients treated without diversion, but our 0% leak rate in 110 patients with a diverting ileostomy is remarkable, especially as we had exclusively treated patients with chronic inflammatory bowel disease, which are known to experience more local septic complications than patients without inflammatory diseases.[5]

Overall, the low rate of local septic complications in our series raises the question whether the broad use of protective ileostomies is really mandatory. Grobler et al.[10] found in a randomized trial that restorative proctocolectomy can be performed without a protective ileostomy in selected patients without increase in the incidence of local septic complications, and Heuschen et al.[25] found a lower rate of complications in selected patients after one-stage procedures as compared to two-stage procedures in a matched-pair analysis. A low incidence of local septic complications in selected patients with IPAA is also confirmed by the 21 one-stage patients in our series. Additionally, the analysis of cumulative morbidities demonstrates that the highest morbidity rates where found for patients who had three-stage procedures. In fact, these patients present a negative selection. However, morbidity of ileostomy closure contributed significantly to the cumulative morbidity of the two- and three-stage operations. In the literature, ileostomy closure is associated with a mortality of 0–2%,[47–50] a morbidity of 11–33%,[49–52] and a leak rate of 1–3% in most[47,48,51,52] but up to 9% in some trials.[50,53] Thus, omitting an ileostomy has some very attractive aspects. If further trials confirm the idea of anastomotic protection by mesorectal preservation, this technique might also allow us to treat more patients with one-stage procedures, and maybe, some of the patients that have so far been treated with three-stage procedures can safely be treated with two-stage procedures.

Aside from these potential effects on the safety of the IPAA, mesorectal preservation has a second potential advantage: Staying away from the pelvic nerves might reduce the risk of postoperative sexual and bladder dysfunction, affecting up to 19.8% of the patients after IPAA in some series.[60] Retrograde ejaculation has repeatedly been described with an incidence of 1.2–4%[21,61,62] or even higher.[63] We did not systematically record sexual and bladder function, but the fact that none of our patients had significant urinary retention can at least be interpreted as one indicator of pelvic autonomic nerve preservation.

One disadvantage of mesorectal preservation could be that functional results in terms of frequency of defecation, urgency, or incontinence might be worse because of a reduced capacity of the pouch when located in a narrow funnel of mesorectal fat. Indeed, the median frequency of defecation was slightly higher than reported by others, but the incidence of urgency was lower.[1,4] The median Vaizey incontinence score of 3 in our series was significantly lower than the score of 7 presented by Heuting et al.[60] for their cohort of 111 patients with IPAA. Therefore, overall, the functional data were similar to those of other comparable trials. Finally, our recently published physiology examinations demonstrated pouch capacity and compliance values within the normal range,[64] indicating that mesorectal preservation is unlikely to reduce the pouch function.

In summary, our data show that restorative proctocolectomy with handsewn anastomosis can be performed with low specific morbidity. The rate of local septic complications in this series, which is much lower than in most other series published over the last 20 years, might in part result from the preservation of the mesorectal fat. As the technique of rectal dissection is not mentioned in the majority of the trials on restorative proctocolectomy, this theory cannot be verified by a systemic review of the literature. However, the low rate of local septic complications, after handsewn ileoanal anastomosis in our series, asks for a prospective randomized trial on the technique of rectal dissection in restorative proctocolectomy.

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Rectal and Pouch Recurrences After Surgical Treatment for Familial Adenomatous Polyposis

Fabio Guilherme Campos · Antonio Rocco Imperiale · Víctor Edmond Seid · Rodrigo Oliva Perez · Afonso Henrique da Silva e Sousa Jr · Desidério Roberto Kiss · Angelita Habr-Gama · Ivan Cecconello

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Abstract
Background Familial adenomatous polyposis (FAP) is a genetic disease characterized by multiple adenomatous colorectal polyps and different extracolonic manifestations (ECM). The present work is aimed to analyze the outcome after surgical treatment regarding complications and cancer recurrence.
Methods Charts from patients treated between 1977 and 2006 were retrospectively analyzed. Clinical and endoscopic data, results of treatment, pathological reports and information about recurrence were collected.
Results Eighty-eight patients (41 men [46.6%] and 47 women [53.4%]) were assisted. At diagnosis, associated colorectal cancer (CRC) was detected in 53 patients (60.2%), whose average age was higher than those without CRC (40.0 vs. 29.5 years). At colonoscopy, polyposis was classified as attenuated in 12 patients (14.3%). Surgical treatment consisted in total proctocolectomy with ileostomy (PCI, 15 [17.4%]), restorative proctocolectomy (RPC, 27 [31.4%]), total colectomy with ileal-rectum anastomosis (IRA, 42 [48.8%]), palliative segmental resection (1 [1.2%]) and internal bypass (1 [1.2%]). Two patients were not operated on due to religious reasons and advanced disease. Complications occurred in 25 patients (29.0%), more commonly after RPC (48.1%). There was no operative mortality. Local or distant metastases were detected in six (11.3%) patients with CRC treated to cure. During the follow-up of 36 IRA, cancer developed in the rectal cuff in six patients (16.6%), whose average age was higher than in patients without rectal recurrence (45.8 vs. 36.6 years). Five of them have had colonic cancer in the resected specimen. Among the 26 patients followed after RPC, cancer in the ileal pouch developed in 1 (3.8%).
Conclusions (1) Within the present series, FAP patients presented a high incidence of associated CRC and diagnosis was generally established after the third decade of life; (2) operative complications occurred in about one third of the patients, being more frequent after the confection of an ileal reservoir; (3) rectal cancer after IRA was detected in 16.6% of patients and it was associated with greater age and previous colonic carcinoma; (4) both continuous and long-term surveillance of the rectal stump and ileal pouch are necessary during follow-up.

F. G. Campos · A. R. Imperiale · V. E. Seid · R. O. Perez · A. H. da Silva e Sousa Jr · D. R. Kiss · A. Habr-Gama · I. Cecconello
Colorectal Surgery Division, Department of Gastroenterolgy, University of São Paulo School of Medicine, São Paulo, Brazil

F. G. Campos (✉)
Alameda Jaú, 1477 Apto 111A, São Paulo (SP) 01420-002, Brazil
e-mail: fgmcampos@terra.com.br

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Introduction

Familial adenomatous polyposis (FAP) is an autosomic inherited disease resulting from germinative or acquired

mutations in the tumor suppressor gene APC gene (*adenomatous polyposis coli*), situated on the long arm of chromosome 5q21.[1] Classic FAP is characterized by the development of hundreds of intestinal polyps that, if left untreated, progress to colorectal cancer by the age of 35–40 years. The disease affects various different tissues and characteristically presents a variable biological and clinical behavior.[2] Less commonly, a less severe polyposis derives from a genetic low penetrance mutation in the MYH gene (*human MutY homologue*) of chromosome I, leading to polyp development after forty-years of age.[3]

The malignant potential of non-treated patients requires prophylactic colectomy and familiar screening to minimize cancer risk.[4] Main surgical options are represented either by colectomy with ileorectal anastomosis (IRA) or restorative proctocolectomy with ileal pouch-anal anastomosis (RPC). Indications of proctocolectomy and ileostomy (PCI) are reserved for patients with advanced low rectal cancer, sphincter dysfunction, or impossibility to perform RPC (mesenteric desmoid). When selecting the primary surgery, one must take into account age, site/number of the polyps, location of the mutation and patient willingness to undergo regular checkups.

Before the development of RPC, IRA was performed in the vast majority of patients, leading to an elevated risk of metachronous rectal cancer estimated in 12% to 43% in the literature.[5,6] These artificially high rates include many patients that would probably undergo RPC during the pouch era.[7] Besides this, ileorectal anastomosis still remains an interesting option, especially for young patients with a moderate disease's phenotype and sparse adenomas in the rectum. Furthermore, it is considered a simple and safe technique associated with few complications and good quality of life.[8].

Restorative proctocolectomy is now considered the gold standard for the treatment of FAP patients. However, many reports describing polyps and cancer in the ileal pouch during the last decade have stressed the importance of long-term follow-up and surveillance of these patients.[9,10]

The present work aimed to review our experience with the surgical treatment of FAP, presenting data regarding operative complications and the evolution of treatment options over the years. Special attention was driven to identify clinical, endoscopic, and pathological risk factors eventually associated with the oncological outcome after ileorectal and ileal pouch-anal anastomosis.

Material and Methods

This study contains data from patients with PAF treated in the Colorectal Unit of Hospital das Clínicas in São Paulo (Brazil) from January 1977 and March 2006. Diagnosis was established on the basis of colorectal adenomatous polyps at the colonoscopy, associated or not with extracolonic manifestations of the disease. Unfortunately, we are not able to perform molecular testing for diagnosis in our public hospital.

There were registered data regarding:

a) clinical features (sex, color, age at clinical manifestations and age at surgical treatment, clinical symptoms; findings on physical examination, annotations about retinal CHRPE);
b) endoscopic findings (upper digestive tract, sigmoidoscopy, colonoscopy), radiological (skull Rx, abdominal tomography) and pathological exams;
c) surgical treatment: number of operated patients, character of surgery (curative or palliative), type of procedures, operative findings, surgical complications and mortality;
d) rectal polyps or cancer recurrence after IRA; rectal or pouch tumoral recurrence during follow-up.

The association of polyposis and colorectal cancer was carefully registered after colonoscopic analysis and pathological examination of the specimen. The distribution and density of colonic and rectal polyps were classified as classic (when the colonoscopist used terms such as numerous, many, thousands, "carpet mucosa") or mild (when the description of polyposis contained words like "little", "sparse" or "rare"; or when less than 100 polyps were found).

Patients with associated cancer underwent clinical, biochemical (carcinoembryonic antigen [CEA]) and radiological investigation (computed tomography [CT]) every 4 months during the first 2 years, every 6 months during the third year and twice during the 4th and 5th years. Upper endoscopy was advised every 2–3 years or more commonly depending on gastroduodenal alterations. Pouches were examined every 2 years. Patients with family history of desmoid disease performed CT every 2 years. However, not all patients performed such investigation due to different reasons.

As we never had complaints of mass or bleeding through the stoma, we have not performed ileostomy endoscopy as a routine.

Results

Clinical and Endoscopic

Treated were 88 patients, 41 men (46.6%) and 47 women (53.4%). Average age was 33.0 years (13 to 80) at the beginning of symptoms, 33.7 years (10 to 80) at diagnosis and 35.9 years (15 to 82) at surgical treatment, respectively.

At diagnosis, 53 patients (60.2%) already had colorectal cancer diagnosed at the colonoscopy or by the pathologist. Their average age was higher than those without CRC (40.0 *vs*. 29.5 years). Age did not differ between patients with (n=66%; 33.4 years) or without (n=44%; 34.4 years) family history of polyposis.

Polyposis was considered *mild* in 12 (14.3%) and severe in 72 patients (85.7%) by colonoscopic appearance. They presented greater average age (48.2 *vs.* 33.3 years), lower frequency of extracolonic manifestations (16.6% *vs*.46.5%) and equal incidence of CRC (58.3% *vs*. 58.3%) compared to those with classic polyposis.

Surgical

Two patients were not operated for other reasons. Regarding the character of surgical treatment, six operations (four total resections, one partial resection, and one derivation) were considered palliative. Surgical procedures are listed in Table 1.

Operative procedures comprised 15 PCI, 27 RPC, 42 IRA, one palliative SR, and one internal derivation. Among the 12 patients classified as having attenuated polyposis, IRA was performed in nine, PCI in two, and RPC in only one patient.

Figure 1 presents the percentages of operative procedures performed in five consecutive periods.

Operative morbidity was registered in 25 patients (29.0%), being 17 (19.7%) before the 30° postoperative day and eight (9.3%) after that period (Table 2). Statistical analysis (Chi-square, p=0.03) showed that RPC complications (48.1%) were significantly greater than PCI (26.6%) and IRA (19.0%), and that PCI and IRA results were similar (p=0.5).

Rectal and Pouch Recurrences

Complete follow-up comprised 12 (80%) PCI, 36 (85.8%) IRA, and 26 (96.3%) RPC patients. Average postoperative follow-up periods for PCI, IRA, and RPC were 49 (4 to 240), 91.1 (3 to 557) and 50.8 months (5 to 228), respectively.

Rectal polyps were detected and resected in 26 (72.2%) patients and rectal cancer in six (16.6%) in IRA patients. After RPC, we detected adenomatous pouch polyps in three (11.5%) and pouch cancer in two (7.6%). These numbers are presented in Table 3.

Table 4 presents the clinical characteristics of patients that presented cancer recurrence in rectal stump after IRA.

Time interval after colectomy varied from 34 to 132 months (58.6 months). Average age was 45.8 years during ileorectal anastomosis and 50.6 years at rectal stump cancer diagnosis. This average was significantly greater (p<0,05) than that observed among patients that did not had rectal recurrence (36.6 years, 17–82).

All patients had rectal polyps at primary surgery or developed them during follow-up. Regarding polyposis severity, only two patients were initially classified as mild form. Five patients presented colonic cancer in the surgical specimen. Surgical treatment after recurrence was represented by local resection in two and proctectomy in three; one patients was not operated on due to disseminated disease to the liver.

Rectal cancer risk after IRA was estimated by Kaplan–Meier's method. The cumulative risk was 17.2% after 5 years, 24.1% after 10 years and 43.1% after 15 years of follow-up. Age-dependent cumulative risk starts after 30 years (4.3%), going to 9.6% at 40 years, 20.9% at 50 years and 52% at 60 years (Figs. 2 and 3).

Discussion

The almost inevitable polyp degeneration is the most relevant clinical feature of FAP.[11] The incidence of CRC out of screening programs may be higher than 60%,[12] similarly to the rate found in this series (60.2%). This is due to the fact that substantial proportion of FAP family members do not agree to perform colonoscopy, despite been informed about the benefits of CRC surveillance.[13]

As the risk of developing cancer in FAP patients increases with age, it was not surprising that patients with concurrent cancer were older (40 vs. 29.5 years). This fact raises the importance of familiar screening during the second decade of life so they may undergo prophylactic colectomy before cancer development. When dealing with older patients, the surgeon must be aware

Table 1 Temporal Distribution of Operative Procedures (86 Patients)

Operative procedures	PCI *N* (%)	IRA *N* (%)	RPC *N* (%)	SR *N* (%)	ID *N* (%)
Total	15 (17.4)	42 (48.8)	27 (31.4)	1 (1.2)	1 (1.2)
Before 1985	2	9	2		
1986 to 1990	1	7	2		
1991 to 1995	1	13	1	1	1
1996 to 2000	5	9	10		
2001 to 2006	6	4	12		

PCI total proctocolectomy with ileostomy, *IRA* total colectomy and ileorectal anastomosis, *RPC* restorative proctocolectomy, *SR* segmental resection, *ID* internal derivation

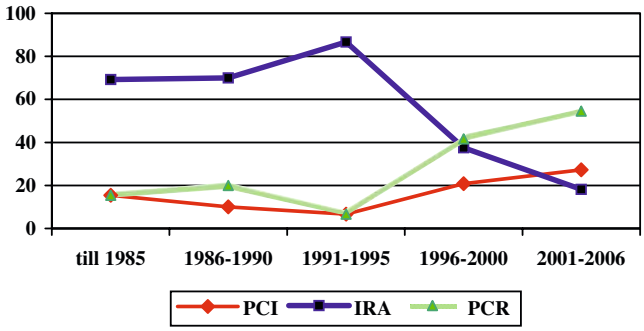

Figure 1 Percent distribution of surgical procedures performed over five consecutive periods.

of this risk and perform an oncological resection of the colon and rectum.

The chance of developing CRC is also related to the polyposis severity,[14] which usually reflects the mutation site.[15,16] Recently, a subset of FAP patients with a milder course of disease termed attenuated familial adenomatous polyposis (AFAP) has been described.[17] Among our 84 patients colonoscopies, a mild form of the disease was found in 12 patients (14.36%).

Compared to the classic FAP, these patients presented greater average age (48.2 *vs*. 33.3 years) and lower frequency of extracolonic manifestations (16.6% *vs*.46.5%), features that are common among attenuated FAP. Furthermore, the extracolonic manifestations found in this group were hyperplasic fundic gastric polyps (1) and CHRPE (1).

Regarding the surgical alternatives to FAP,[18,19] IRA is considered an easy technique associated with a low rate of complications and good functional results.[5,20] This indication is especially interesting in AFAP, being performed in nine out of 12 patients of our series that were considered to have a mild disease. RPC is nowadays the most common operative procedure, as it carries a low mortality (0.5–1%) and an acceptable risk of non-life-threatening complications (10–25%).[21]

Among our 86 patients, PCI was performed in 15 (17.4%), IRA in 42 (48.8%), and PCR in 27 (31.4%). Operative morbidity was registered in 25 patients (29%), being more common after proctocolectomies (RPC 48.1%; PCI 26.6%) than after IRA (19%). We observed 17 (19.7%) early and 8 (9.3%) late complications. The early ones were represented by cardiopulmonary problems (two patients), abdominal wall infection (three), anastomotic leakage/fistula (six), pelvic abscess (one), intestinal obstruction (one), and others (four). These complications required reoperation in three patients. There was no mortality.

Complications after discharge were intestinal obstruction (four for adherences and one after ileostomy closure), one anastomotic stenosis, one pouch-vaginal fistula, and one urinary incontinence. Three patients with obstruction and one with fistula were treated surgically.

In a recent revision by metanalysis,[8] 1,002 patients from 12 studies were compared. There was a greater reoperation rate for RPC (23.4% *vs*. 11.6%) and no differences regarding sexual dysfunction or operative complications. Rectal cancer after IRA was detected in 5,5% of patients. In the literature, the reported incidence of metachronous rectal cancer varies from 12 to 43%.[5,22] After 10 years, the risk is 5–12%, going to almost 25% after 15–20 years.[23–29] Data from the Polyposis Registry in Sweden indicate a 25.7% cumulative risk at 70 years of age.[30] Pathology (presence of villous adenomas, dysplasia, polyps number, size, and shape) and APC gene mutation locus have also been associated with this risk.[30–33]

During an average follow-up of 91 months (three to 57), six out of 36 IRA patients (16.6%) in the present series developed rectal cancer. Median ages at primary colectomy for FAP and at rectal cancer diagnosis were 45.8 and 50.6 years, respectively. Time interval varied from 34 to 132 months (average 58.6 months).

This median age was significantly greater than that observed among IRA patients who did not develop rectal cancer (36.6 years, 17–82). We observed that cancer risks increase with time after surgery, and consequently with age. As the average follow-up was long enough (91 months), we believe that this difference would be the same irrespective of length of follow-up. So, age at diagnosis and treatment is one of the main predictive factors involved in rectal cancer development after IRA. The cumulative cancer risk was 17%, 24%, and 43% for 5, 10, and 15 years, respectively. Regarding age, this risk started at 30 years (4.3%) and increased to 9.6% at 40 years, 20.9% at 40 years and 52% at 60 years.

In the St. Mark's Registry,[22] the cumulative risk increased from 10% at 50 years to 29% at 60 years, similar to

Table 2 Operative Complications in 86 Patients

Complications	PCI (15) *N* (%)	IRA (42) *N* (%)	RPC (27) *N* (%)	SR (1) *N* (%)	ID (1) *N* (%)
Early	01 (6.6)	07 (16.6)	09 (33.3)	0	0
Late	03 (20.0)	01 (2.4)	04 (14.8)	0	0
Total	04 26,6	08 19,0	13 48,1	0	0
Chi-square	PCI = IRA	RPC>IRA	RPC>PCI		
p	*p*=0.5	*P*=0.03	*P*=0.03		

PCI total proctocolectomy with ileostomy, *IRA* total colectomy and ileorectal anastomosis, *RPC* restorative proctocolectomy, *SR* segmental resection, *ID* internal derivation

Table 3 Polyps and Cancer Recurrence after Ileorectal Anastomosis or Ileal Pouch Anastomosis

Procedure	Follow-up	Polyp recurrence	Percent	Cancer recurrence	Percent
IRA (n=42)	36	26	72.2	6	16.6
RPC (n=27)	26	3	11.5	1	3.8

IRA total colectomy with ileorectal anastomosis, *RPC* restorative proctocolectomy.

the numbers found in North Europe (26% at 65 years).[23] These data raises the need for a rigorous preoperative selection of patients considered candidates for IRA.

This risk also exists for those with mild disease. Two patients had rectal cancer after primary colectomy at 47 and 56 years, suggesting that the age may have an important role even in these patients. Eventually, the indication of IRA before 30 years may allow them to live about 20–25 years before developing a cancer in the rectal stump.[22] Although five of the patients presented colonic cancer at the first operation, it is not known if this finding increases the chance of a rectal cancer or if it is only associated with the progressive age.

The number of rectal polyps has been traditionally used as important criteria to help surgical decision,[34] sometimes in association other features such as size/gross appearance[35,36] and individual/family genotype.[33] The number of lesions associated with greater risk is still a matter of debate, although most believe that less than 10 rectal polyps at presentation can predict a favorable outcome after IRA.[35–37]

In an interesting study with 213 patients, Church et al.[34] tried to correlate the findings at preoperative proctoscopy with the polyposis severity and postoperative outcome. Patients with less than five polyps were frequently asymptomatic (73%), had mild polyposis in 86% and were treated by IRA (92.5%). Only 6.9% required proctectomy, none of them to treat cancer. Seven patients (of 128) with less than 19 rectal adenomas and less than 1.000 colonic adenomas needed proctectomy.

On the other hand, 35% of IRA patients with more than 20 rectal adenomas and more than 1.000 colonic adenomas had proctectomy, four of them (10.8%) due to cancer. Patients with 6–19 adenomas had intermediate results. So, it seems that less than five rectal adenomas indicates mild disease and good outcome after IRA.

The same authors[5] compared patients operated from 1959 to 1983 (when RPC was not an option) to others treated from 1983 to 1999. Proctectomy was necessary in 32% of the first group when compared to 2% of patients treated in the era of ileal pouch. Patients did not differ in average age (23 years), rectal stump length (14.3 *vs*. 14.7 cm) and incidence of severe polyposis (49 *vs*. 44%).

For many, the risk of rectal cancer after IRA means that RPC should be recommended for the vast majority of FAP patients. Exceptionally, one could propose a primary IRA followed at a later age by a secondary proctectomy with RPC for some selected cases on the basis of clinical, genetic data, and patient will with regards to female fecundity.[21]

The work published by the Swedish Polyposis Registry [38] reported the experience with 120 patients. Complications occurred in 51% after RPC: No cancer occurred either in the ileal pouch or in retained rectal mucosa. IRA lead to complications in 26% and rectal cancer in 4.7%. The authors concluded that IRA determined good surgical and functional outcome that should be taken into consideration against the low excision rate of pouch surgery.

The series from the Mount Sinai Hospital in Toronto[19] compared 50 RPC (mean age 35 years; follow-up 6 years) against 60 IRA (mean age 31 years; follow-up 7.7 years). There were no statistical differences with respect to anastomotic leak rate (12 vs. 3%), risk of small bowel obstruction (24% vs. 15%), risk of intra-abdominal sepsis (3% vs. 2%) and reoperation rate (14% vs. 16%). Twenty-one patients (37%) with IRA were converted to ileal pouch-anal anastomosis (12) or proctocolectomy (nine), because of rectal cancer (five patients), dysplasia (one patient), or uncontrollable rectal polyps (15 patients). They concluded that IRA is still an option for those with rectal polyp

Table 4 Clinical Data from Patients with Recta Recurrence After IRA

Sex	M	F	F	M	M	M
Initial age	27	35	47	63	56	47
Interval	48 m	42 m	132 m	48 m	34 m	48 m
Rectal polyps	Present	Present	Present	Present	Present	Present
Colonic polyposis	Severe	Severe	NA	Severe	Attenuated	Attenuated
Colon cancer	Yes	Yes	Yes	Yes	Yes	No
Other cancer	No	No	Stomach	Lymphoma	No	No
Treatment	LR	PT	PT	LR	PT	NO
Pathology	T1N0M0	T3N0M0	T2N0M0	T1N0M0	T3N0M0	M1

M male sex, *F* female sex, *m* months, *NF* data not available, *PT* proctectomy, *LR* local resection, NA data not available

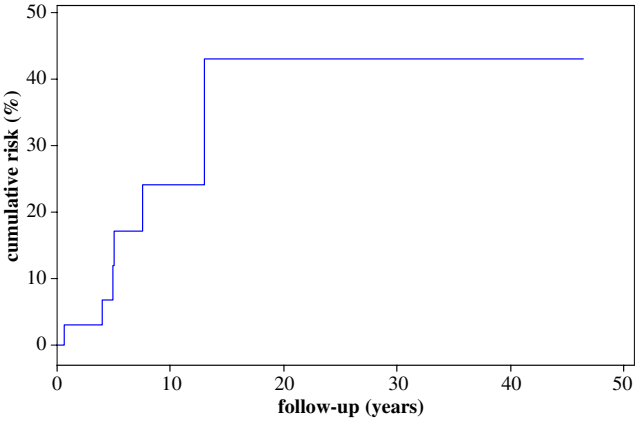

Figure 2 Cumulative risk for rectal stump cancer after IRA and follow-up.

sparing and good compliance for follow-up, but emphasize that RPC leads to a lower long-term failure rate.

Another interesting view came from the clinical and pathological data collected in four national polyposis registries.[6] In a group of 659 IRA, 47 (7.1%) developed rectal cancer and the risk of dying from rectal cancer was 12.5% by age 65. Compared with IRA, RPC would lead to an increase in life expectancy of 1.8 years. Furthermore, 75% of patients with rectal cancer had a negative rectoscopy within 12 months before diagnosis, showing that follow-up examinations do not provide efficient protection against rectal cancer.

As we stated before, RPC indications in our series have gradually became more common compared to IRA, mainly due to the selective indications of these procedures in the face of the disease's characteristics. Since its introduction by Parks and Nicholls[39] in 1978, RPC has been considered the treatment of choice for FAP, based on the idea that it eliminates the risk of malignant transformation and provides good functional results[22,35,40] especially in younger patients.[41]

Compared to the known oncological concerns after IRA, the risks of late degeneration and the long-term surveillance after RPC have not been adequately emphasized so far. Against the premise that it eliminates cancer risk above, there is accumulating evidence that adenomas develop in the pouch in about 8% to 60% of the cases,[22,42,43] range that is much higher than the 9–25% incidence of adenomas in the preoperative ileum of patients with FAP.[44,45] These numbers imply the idea that the development of adenomas is accelerated in the ileal pouch of patients with FAP,[46] although others found that mucosal dysplasia is uncommon.[47] Furthermore, the description of less than 10 pouch adenocarcinomas so far[9,10,48,49] may indicate that RPC does not eliminate the risk of malignization. So, the tradeoff of neoplasia control in FAP patients seems to be much more complex than previously thought.

Ileal adenomatosis transformation, number of pouch adenomas, age, incomplete mucosectomy, altered cell kinetics due to intraluminal changes leading to metaplasia–displasia–neoplasia sequence have been enrolled as possible carcinogenic mechanisms after RPC.[9,46,50–52] Our group has personally witnessed one case that represent 3.8% of our RPC cases.[9]

Another source of concern for FAP patients is the development of ileostomy carcinomas. A revision of this rare complication estimates less than 40 cases of cancer at that site after proctocolectomy.[53,54]

Thus, the cancer recurrence risks during follow-up show that FAP is a complex disease with multiple variations that do not fit into one management scheme. This wide clinical variability is generated by the genetic load that may impact oncological outcome and the choice of surgery. This fact demands that experienced specialists may preferably manage FAP, as the decision-making process may not be simplified to the conventional discussion about pros and cons of IRA *versus* RPC. This discussion has to involve a number of issues such as age, genotype, sphincter function, presence/absence of desmoid disease, potential complications that might ensue from each procedure and risk factors for tumor recurrence.

Although some series indicate that IRA is not the best operation for FAP, important considerations must be taken into account on an individual basis. Potential candidates for IRA are represented by younger individuals with few polyps and a mild phenotype family history, patients with attenuated disease and those who refuse to undergo a temporary ileostomy for pouch [5,37]. When deciding in favor of IRA, one must be aware that regular examinations may not necessarily detect eventual rectal cancers and that risk for rectal cancer increases with time, age and is probably related to previous colonic carcinoma.[38]

The presence of dense polyposis and family history or mutation associated with severe polyposis should trend the choice toward an ileal pouch anastomosis. RPC complica-

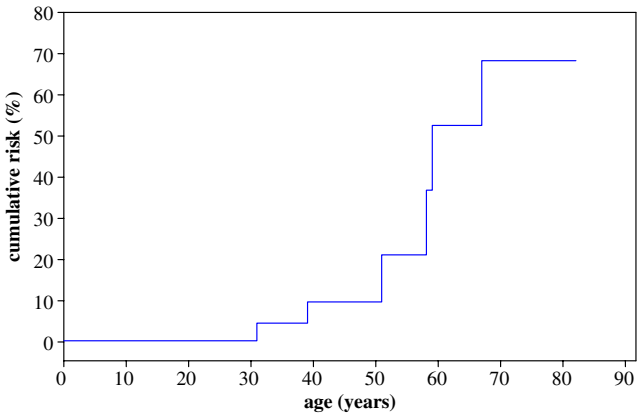

Figure 3 Age-dependent cumulative risk for rectal cancer after IRA.

tions are common, but mortality rates are low. When thinking about RPC, is important to remember that not all surgeons achieve the same functional results with RPC as with IRA and that RPC may affect fertility of female patients.[55]

Another important issue is the timing of the surgical treatment. A practical situation such as convincing an asymptomatic girl during her "golden years" of youth and social development to undergo a major surgery (that may require a temporary stoma and increase the number of daily evacuations) is a hard task. So, the correct approach to this problem may be crucial to the patient's and family's compliance.

Whenever available, the presence of specific mutations related to severe disease, cancer and desmoid tumors can influence the final decision. But until the genetic information become widely available, the current knowledge about oncological outcome strengthens the recommendation for regular and long-term surveillance after any kind of operative procedure performed.

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Death after Bowel Resection: Patient Disease, Not Surgeon Error

Neil H. Hyman · Peter A. Cataldo · Elizabeth H. Burns · Steven R. Shackford

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Abstract
Introduction Although bowel resection is associated with a significant mortality rate, little is known about the demographics of the patients and how often surgical error is the primary cause of death. We sought to use a rigorous prospective quality database incorporating standardized peer review, to define how often patients die from provider-related causes.
Materials and Methods All patients undergoing bowel resection with anastomosis at a university hospital from July 2003 to June 2006 were entered into a prospectively maintained quality database. Patients were seen daily with house staff by a specially trained nurse practitioner who recorded demographics and complications. Clinical case reviews were conducted monthly. Five hundred sixty-six patients underwent bowel resection with anastomosis during the study period.
Discussion One hundred ninety-three patients suffered at least one complication (34.1%) and there were 20 deaths (3.5%). In 17 cases, death was deemed unavoidable due to patient disease; most occurred in patients who developed ischemic bowel while hospitalized for a serious concomitant illness. In only one case did death appear clearly related to a surgical complication (0.17%). Death after bowel resection typically reflects the need for urgent surgery in extreme circumstances and not surgeon error. Postoperative mortality rate in this population appears to be poor indicator of surgical quality.

Keywords Bowel resection · Mortality · Quality · Complication

Introduction

Intestinal resection with anastomosis is a major surgical procedure associated with a considerable morbidity and mortality rate.[1] However, relatively little is known about the demographics and clinical characteristics of patients who die postoperatively. The substantial variation in the reported 30-day surgical mortality[2–8] implies that many of these deaths may be preventable and could be attributable to surgeon error.

We sought to utilize our rigorous, prospective quality database incorporating standardized peer-review to determine how often patients die from provider related causes versus unavoidable deaths from inherent patient disease.

Materials and Methods

All adult patients undergoing partial resection of the small or large intestine with anastomosis from July 2003 through June 2006 at Fletcher Allen Health Care, the teaching hospital of the University of Vermont College of Medicine, were entered prospectively into the surgical activity tracking system (SATS) quality database. This included CPT codes 44202, 44204, 44205, and 44207 for laparo-

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N. H. Hyman · P. A. Cataldo · E. H. Burns · S. R. Shackford
Department of Surgery,
University of Vermont College of Medicine,
Fletcher Allen Health Care,
Fletcher House 301, 111 Colchester Avenue,
Burlington, VT 05401, USA

N. H. Hyman (✉)
Medical Center Hospital of Vermont, Department of Surgery,
University of Vermont College of Medicine,
Fletcher 301, 111 Colchester Avenue,
Burlington, VT 05401, USA
e-mail: Neil.Hyman@vtmednet.org

scopic cases and 44120, 44140, 44145, and 44160 for open procedures. All patients had a datasheet created upon admission to the hospital with relevant demographics entered. Patients were seen daily with house staff by a specially trained nurse practitioner who recorded complications as they occurred. Clinical case reviews were typically conducted twice monthly on all patients who suffered a complication or death by a team of gastrointestinal surgeons, house staff and the nurse practitioner along with the treating physicians. Details of the SATS have been fully described elsewhere.[9]

Based on peer review, deaths were ascribed to patient disease, provider-related causes, or a combination. If the death appeared unavoidable owing to the nature of the patient's disease state and comorbidities, and the medical decisions and care rendered were deemed appropriate, the death was recorded as due to patient disease. When potentially preventable complications were identified that were thought to be significant contributors to the patient's death, the mortality was recorded as provider-related. When potentially preventable complications were observed with an uncertain or peripheral role to the patient's demise, the death was attributed to a combination of the two. Secondary chart review was then performed on all patients who died to determine whether the procedure was performed electively or on an urgent/emergent basis. Patient demographics, indications for surgery, comorbidities, procedure performed, length of stay, complications, and peer review adjudication were recorded. Opportunities for improvement were discussed and process changes were made as considered appropriate.

Results

Five hundred sixty-six patients underwent one or more bowel resections with anastomosis during the study period (Table 1). One hundred twelve procedures (25.2%) were performed laparoscopically. One hundred ninety-three patients suffered one or more complications (34.1%) and there were 20 deaths (3.5%). Eighteen of the deaths (90%) occurred following urgent/emergency surgery. In 17 cases, death was deemed unavoidable due to patient disease; most occurred in patients who developed ischemic bowel while hospitalized for a serious concomitant illness (Table 2).

Table 1 Distribution of Intestinal Procedures (n=566)

	Laparoscopic	Open
Small bowel resection	9	112
Large bowel resection	35	126
Ileocolic resection	35	69
Anterior resection	42	97
Multiple	0	41
Total	121	445

There was one provider-related death. This was a 72-year-old male with a locally advanced gastric cancer who underwent an en bloc transverse colectomy at the time of his gastrectomy. He developed a postoperative leak from his colonic anastomosis with subsequent failure to thrive and died approximately 1 month postoperatively. In two cases, provider-related complications were believed to have contributed to the patient's death. In one case, a patient developed septic shock with ischemic small and large bowel after an esophageal resection, requiring reoperation. This man developed a leak from his colonic anastomosis postoperatively and never recovered. It was uncertain whether the leak and subsequent fistula contributed substantially to his death; however, the anastomosis was deemed unwise in the setting of ischemic bowel disease and the death was therefore adjudicated as partly attributable to provider-related causes. In the second case, a patient with severe coronary artery disease and metastatic lung cancer developed a postoperative abscess after a palliative small bowel resection for malignant obstruction. He died 3 weeks later from an apparent arrhythmia; since the abscess prolonged his hospital stay, provider-related factors were thought to have contributed to his death.

The median survival after surgery in the patients who died was 20 days, (range 0–111 days). Five of the deaths occurred in the first 3 days postoperatively and five of the deaths occurred more than 30 days postoperatively (Fig. 1). All patients who died postoperatively had at least one complication recorded (median, 5; range, 0–11).

Discussion

Our data suggests that death after intestinal resection with anastomosis typically occurs in severely ill patients who require urgent surgery for an intra-abdominal catastrophe. Death after elective surgery occurred in only two cases. In only three cases (0.5%), did a surgeon-related complication appear to play a role in the postoperative mortality. Further, in two of these three cases, it is uncertain whether or not this complication was a major factor in the patient's demise.

We do not assert that we did not make technical or judgment errors in the care of our patients in this series. In fact, the complication rate of 34.1% is considerable and opportunities to improve our processes and performance undoubtedly exist. Further, even a single preventable death should not be accepted. These tenets are central to our quality process, and the SATS tracking system has indeed been shown to have reduced morbidity rates and improved outcomes at our institution.[9] It is simply that these

Table 2 Clinical Characteristics of Patients who Died After Bowel Resection (n=20)

Diagnosis	Major preoperative morbidity	Elective (E) vs urgent (U)	Adjudication
	Small bowel resection (n=10)		
Ischemic bowel	Following aortic valve replacement	U	PD
Ischemic bowel	Atrial fibrillation	U	PD
Ischemic bowel	Atrial fibrillation, renal failure	U	PD
Ischemic bowel	Severe coronary artery disease, s/p toe amputation	U	PD
Ischemic bowel	Atrial fibrillation	U	PD
Ischemic bowel	Multiorgan failure, following esophagectomy for cancer	U	PD
Malignant obstruction	Metastatic lung cancer/comfort care	U	PD
Malignant obstruction	Metastatic bile duct cancer/comfort care	U	PD
Malignant obstruction	Metastatic lung cancer, severe coronary artery disease	U	C
Hemorrhage	Pneumonia, respiratory failure	U	PD
	Large bowel resection (n=8)		
Ischemic bowel	Following repair aortic aneurysm	U	PD
Ischemic bowel	Following coronary artery bypass graft	U	PD
Ischemic bowel	Atrial fibrillation	U	PD
Ischemic bowel	Severe coronary artery disease	U	PD
Malignant obstruction	Congestive heart failure	U	PD
Perforated colon cancer	Peritonitis, shock	U	PD
Recurrent diverticulitis	Severe coronary artery disease, ventricular fibrillation, intractable pain	E	PD
Locally advanced gastric cancer	Colon invasion	E	PR
	Small and large bowel resection (n=2)		
Ischemic bowel	Following esophagectomy for cancer	U	C
Ischemic bowel	Severe pancreatitis	U	PD

PD Patient disease, *PR* provider related, *C* combination of patient and provider-related factors

complications do not often lead to the death of an otherwise healthy patient.

Our results may not be typical of other institutions and, therefore, not generalizable. However, our mortality rate (3.5%) appears to be consistent with population-based series of intestinal resections reported in the literature.[2–6] As others have noted, there is a marked difference between the colon mortality rate that is typically reported in case series versus population-based data.[8–10]

If our data represents a typical institutional experience, the implications would be highly relevant to efforts at quality measurement and improvement for intestinal surgery. Eighty-five to 95% of deaths after intestinal resection were deemed unavoidable; this implies that structural and process improvements are unlikely to impact the surgical mortality rate after intestinal resection. Postoperative mortality in this series was an indicator of case mix (operating on extremely ill patients with minimal chance of survival) and not reflective of suboptimal care. As such, physician "report cards" that report surgical mortality for intestinal resection are not likely to be useful guides to surgical quality after bowel resection and, in fact, may be misleading. The variation in surgical mortality for bowel resection reported from analyses of administrative databases could be attributable to confounding by patient characteristics and not fairly attributed to defects or variability in the quality of care. The deficits of administrative databases in this regard have been recognized.[11–14]

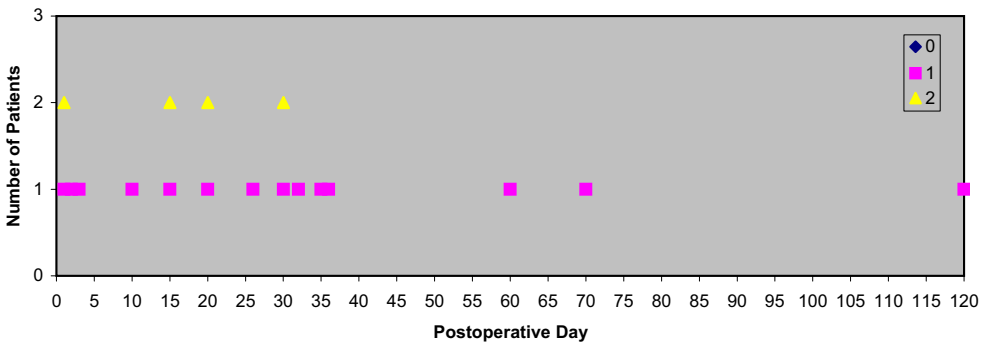

Figure 1 Timing of death after surgery in patients who died after bowel resection with anastomosis.

Another interesting finding from our case reviews was that the recording of "complications" in patients who die postoperatively does not usually indicate that they contributed to their death; the apparent association between complications and death can be misleading if taken out of context. The majority of the complications we observed in these patients were associated with the process of dying and occurred after "the die were cast". Prior to death, patients often have organ failure, biochemical evidence of a myocardial infarction, or an arrhythmia that simply represents the process of dying, not complications that led to death.

We believe that individual case review by a group of peers with the treating physicians is a superior methodology for understanding where defects in quality care exist, rather than relying on speculative explanations of associations detected from large discharge databases. First, it is remarkable how often these discharge datasets and even chart entries are inaccurate or at least do not truly reflect what actually happened to the patient. For example, Richardson noted a 68% error rate when data from administrative sources was compared to chart review on the same patients with abdominal aortic aneurysms[15] or carotid disease,[16] noting there was "virtually no correlation between the data sources".[17] We have previously demonstrated that the hospital discharge data set at our institution missed 28% of the complications recorded in our surgical activity tracking system.[18]

Even if the data in these registries is accurate and complete, it is still difficult to be sure how often variation in outcomes reflect problems in the quality of care, let alone try and identify where opportunities for improvement exist.[19] For example, it has been shown that only 51–65% of patients with stage II or III rectal cancer receive radiation therapy as recommended by the NIH Consensus Conference Standards.[20–22] One could conclude that surgeons are not sufficiently familiar with the guidelines and need to be "educated". Yet in our statewide[10] and regional[23] colorectal cancer quality projects, 100% of stage appropriate were offered or at least considered for adjuvant therapy. When patients did not receive radiation, it was because they did not wish to be treated or because it was not thought to be in their best interest based on comorbidities.[24] Knowing what actually happened to the individual patient and why certain judgments were made "on the ground" are critical to identifying true gaps in quality and designing rational quality improvement processes.

Even risk-adjusted databases have important limitations. The assumption that risk adjustment levels the playing field has been labeled a "common misinterpretation" and may not allow valid hospital-to-hospital comparisons.[25] A hospital may find itself in the upper quartile of performance in one risk-adjusted database, and in the lowest quartile in another risk-adjusted database. Even if we accept the data interpretation, it is uncommon for any individual provider to have the volume necessary for individual performance assessment and there is limited information to guide practice improvement. Peer review case analysis with the treating team facilitates the identification of instances when evidence-based processes were not used, or when remediable errors in judgment and/or technique contributed to or caused a complication. It moves the process beyond the relentless questions concerning data validity and makes the surgeons central to the quality improvement process.

It is vital to point out that our data does not in any way imply that the care of surgical patients undergoing bowel resection cannot be improved. Complications are expensive, cause considerable patient suffering and often impair the functional outcomes of surgery.[26] Rather, in our experience, they do not often result in the death of a patient who truly had a reasonable prospect of postoperative survival. Mortality rate, although an easily defined and measured endpoint may simply be a poor indicator of surgical quality, at least for intestinal resection.

One cannot conclude from our data that most of these deaths were truly unpreventable since many were necessitated by complications that occurred after other operations or treatment of other serious illnesses. For example, poor myocardial preservation or suboptimal management of a patient who developed ischemic bowel after a coronary artery bypass procedure may lead to the need for intestinal resection. Rather, it seems inappropriate to attribute the death to the surgeon who removed the ischemic bowel if his/her care appeared to be optimal.

Conclusion

In summary, our data suggest that mortality rate, by itself, is a poor indicator of the quality of care rendered to patients requiring intestinal resection with anastomosis. Death most reflects severity of illness, acuity, and comorbidities in patients undergoing surgery for an intra-abdominal emergency. As such, using mortality rates after bowel resection as an indicator of surgical quality is likely to be misleading.

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The Spectrum of Abdominal Tuberculosis in a Developed Country: A Single Institution's Experience Over 7 Years

Ker-Kan Tan · Kenneth Chen · Richard Sim

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Abstract
Background The incidence of human immunodeficiency virus (HIV) infection is rising, and as a result, tuberculosis (TB) has become a resurgent problem in many developed countries.
Objectives The aim of this study was to review the spectrum of abdominal TB and its surgical management in our institution.
Methods A retrospective review of all abdominal TB cases notified to the health authorities by our institution from Jan 01 to Oct 07 was performed.
Results There were 57 patients (37 men) with abdominal TB, with a median age of 47 (range 14–74) years. Active pulmonary TB was present in 27 patients (47%). Positive HIV status was present in 30% and untested in 58%. The majority of patients underwent computed tomography scans (n=50, 88%). The main radiological findings included bowel thickening, lymphadenopathy, ascites, free gas suggestive of perforation, and abscesses. The diagnosis of TB was confirmed on microbiological and/or histological examination in 72%, while the remaining 28% were diagnosed based on the clinical presentation and radiological imaging. All patients were commenced on anti-tuberculous therapy. TB involved the small or large bowel in 33 patients, mesenteric lymphadenopathy in 24, peritoneum in 13, spleen in seven, pancreas in two, anus in two, and the liver in two. Disseminated (including pulmonary) TB occurred in 27 patients (47%), while isolated intra-abdominal TB occurred in the remaining 30 patients (53%). Twenty-five patients (44%) underwent surgery—16 laparotomies (six perforated viscus, five intestinal obstruction, three suspected malignancies, and two for suspected acute abdomen), five laparoscopic procedures (four diagnostic, one gastrojejunostomy bypass for gastric outlet obstruction), two appendicectomies, one drainage of abscess, and one anal fistulotomy.
Conclusions Although TB is eminently treatable medically, surgery is still often required for suspected or confirmed abdominal TB presenting with acute complications or as atypical diagnostic problems. The role of laparoscopy is likely to be more significant in future in the management of abdominal TB.

Keywords Tuberculosis · Abdominal · Surgery · HIV

Introduction

The World Health Organization (WHO) has estimated that there are approximately 8.8 million new cases of tuberculosis (TB) each year with an annual mortality of over 1.6 million.[1] The increased prevalence of human immunodeficiency virus (HIV) has accelerated the gravity of this epidemic.[2] Abdominal TB can infect the gastrointestinal tract, peritoneum, mesentery, abdominal lymph nodes, liver, spleen, and pancreas.[3–5] It also tends to mimic other inflammatory or neoplastic conditions.[6–8] Diagnosis is often delayed due to the lack of specific symptoms and laboratory findings. As a result, effective treatment is delayed with ensuing morbidity and mortality. In this study, we reviewed the spectrum of abdominal TB and its surgical management in our institution.

K.-K. Tan (✉) · K. Chen · R. Sim
Department of General Surgery, Tan Tock Seng Hospital,
11 Jalan Tan Tock Seng,
Singapore 308433, Singapore
e-mail: kerkan@gmail.com

Methods

Study Population

Tan Tock Seng Hospital is a 1,300-bed hospital in Singapore that provides medical care to over 1.5 million people. Our unit is the main surgical referral center for TB and/or HIV patients due to the proximity of both the TB Control Unit and Communicable Disease Centre. All newly diagnosed TB cases are notified and monitored by the Ministry of Health in Singapore. We performed a retrospective review of all patients that were diagnosed with abdominal TB in our institution between January 2001 and October 2007.

Definition

The diagnosis of abdominal TB was established by one of the following criteria: (1) definitive diagnosis—histologic and microbiologic evidence of *Mycobacterium tuberculosis*, the presence of granulomas with caseous necrosis, or successful culture of *M. tuberculosis* from the tissue specimen, or the presence of documented TB in another site with typical operative findings and granulomas; or (2) clinical diagnosis—clinical and radiological features of abdominal TB, responding to antituberculous medication in the absence of definitive diagnosis.

Clinical presentation is extremely varied, and therefore, clinical features alone cannot confirm the diagnosis of abdominal TB. Some of these clinical features include symptoms such as abdominal pain, diarrhea, vomiting, anorexia, weight loss, and pyrexia of unknown origin. The presence of abdominal mass, ascites, or intestinal obstruction is not uncommon.[9]

In our institution, most patients who were diagnosed to have abdominal TB had computed tomography (CT) scan performed. Typical radiologic features of abdominal TB include ascites, thickening of the peritoneum, mesentery, or bowel wall, and lymphadenopathy.[10–13] These lymph nodes are associated with low attenuation centers and enhanced rims suggestive of caseous necrosis.

If clinical suspicion of HIV infection is high, serology and Western Blot test would be recommended to confirm the diagnosis. However, the test could only be performed upon patient's consent after appropriate counseling. All patients with concomitant HIV infection were co-managed with infectious disease physicians, who ensured appropriate treatment for the abdominal TB as well as preventing opportunistic infection.

Results

There were 57 patients (65% males) who were diagnosed with abdominal TB with a median age of 47 (range 14–74) years (Table 1). Two thirds of our patients were ethnic Chinese. The median duration of follow-up was 10 (range 0–21) months. The two main presenting symptoms were abdominal pain (61.4%) and fever (36.8%; Table 2). Twenty-four (42%) patients had their HIV status examined, with 17 (70.8%) of them tested positive. A significant 58% of the patients did not have their HIV status tested. The other important co-morbidities of abdominal TB included end-stage renal failure (10.5%) and long-term immunosuppressant (3.5%). Twenty-seven (47.4%) patients had active pulmonary TB at the time of diagnosis of abdominal TB. The majority of our patients (n=50, 87.7%) underwent CT scans of the abdomen and pelvis (Table 3). The common CT findings included bowel thickening (66%) (Fig. 1), ascites (40%), and lymphadenopathy (48%) (Fig. 2).

Definitive diagnosis was achieved in 41 (71.9%) patients, while in the remaining 16 (28.1%) who were diagnosed clinically, all responded to chemotherapy (Table 2). Antituberculous therapy was started for all patients, with the RHEZ (rifampicin, isoniazid, ethambutol, pyrazinamide) regime most frequently adopted.

Thirty-three (57.9%) patients had TB involving the small and large bowels. There were numerous patients with multiple diseased areas. The two most common regions of bowel involvement were ileum (63.6%) and caecum (48.5%) (Table 4). Other areas included the lymph nodes (42.1%), solid organs (19.3%), and the peritoneum (22.8%).

Twenty-five (43.9%) patients underwent surgery (Table 5). Ten (40%) of them were elective procedures, while 15 (60%) required emergency surgery. Of the ten elective procedures

Table 1 Patients Characteristics

Characteristics	Number of patients (%)
Age	
≤40	24 (42.1%)
>40	33 (57.9%)
Gender	
Male	37 (64.9%)
Female	20 (35.1%)
Racial distribution	
Chinese	35 (61.4%)
Malay	14 (24.6%)
Indian	5 (8.8%)
Filipino	2 (3.5%)
Thai	1 (1.8%)
HIV Status	
Positive	17 (29.8%)
Negative	7 (12.3%)
Unknown	33 (57.9%)
Active pulmonary tuberculosis	
Present	27 (47.4%)
Absent	30 (52.6%)

Table 2 Symptoms of Patients and Diagnosis of Abdominal TB

	Number of patients (%)
Symptoms	
Abdominal pain	35 (61.4%)
Fever	21 (36.8)
Vomiting or diarrhea	16 (28.1%)
Anorexia and weight loss	13 (22.8%)
Abdominal distension	13 (22.8%)
Diagnosis of abdominal tuberculosis	
Histological and Microbiological	5 (8.8%)
Histological only	19 (33.3%)
Microbiological	17 (29.8%)
Clinical diagnosis	16 (28.1%)

(Table 5), four were laparotomies, five were laparoscopies, and one was a fistulotomy. Of the four laparotomies that were performed, three were for suspected malignancy and one for stricture causing intestinal obstruction. Most (n=4, 80%) of the laparoscopic procedures were for diagnostic purposes. The only therapeutic laparoscopic procedure was a gastrojejunostomy bypass that was carried out in a 53-year-old gentleman. He presented with symptoms of gastric outlet obstruction and was subsequently diagnosed with superior mesenteric artery syndrome due to severe weight loss from disseminated TB. Conservative measures failed to reverse his condition. Despite the successful surgery, he passed away a few weeks later from pneumonia.

Of the 15 emergency surgeries (Table 5), laparotomy was performed in 12 patients: six had perforated hollow viscus, four had unresolving intestinal obstruction that were due to the dense tuberculous adhesions or intestinal strictures, and the remaining two had acute abdomen. Another two patients underwent appendicectomy, while the last patient underwent incision and drainage for an abscess.

In our series, the mortality rate was 29.8%. The majority (15 patients) died from disseminated TB, pneumonia, or end-stage renal failure. The other two mortalities were direct consequences of their surgical conditions. The first was a 68-year-old gentleman with perforation of the terminal ileum that required emergency bowel resection; he succumbed to septic shock from peritoneal contamination 2 days later. The other was a 37-year-old woman who underwent emergency right hemicolectomy for intestinal obstruction. This was complicated by anastomotic dehiscence on the fifth postoperative day. She also succumbed to septic shock subsequently.

Table 3 Findings of the 50 Patients Who Underwent CT Scans

CT scan findings	Number of patients (%)
Bowel thickening	33 (66.0%)
Mesenteric lymphadenopathy	24 (48.0%)
Ascites	20 (40.0%)
Free gas suggestive of perforation	2 (4.0%)
Splenic involvement	7 (14.0%)
Liver involvement	2 (4.0%)
Pancreatic head mass	2 (4.0%)

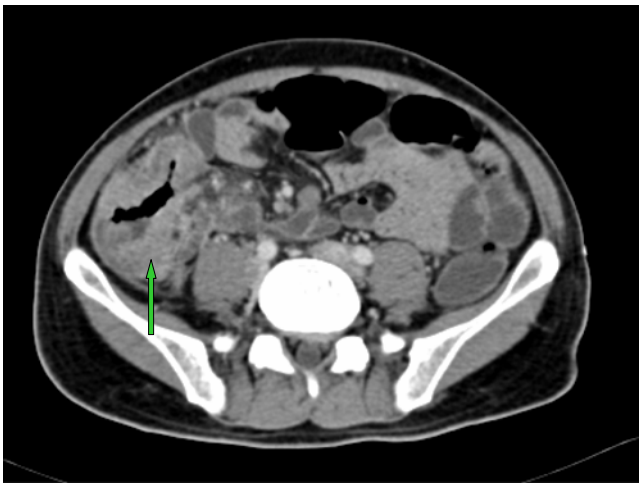

Figure 1 CT Scan showing significant thickening of the ascending colon (*arrow*).

Discussion

TB is seeing a resurgence in recent years due to the increased prevalence of HIV infection.[1,2] HIV is present in up to 50% of patients with TB in developing countries,[14] while patients with HIV are 11 times more likely to develop TB infection.[15] The situation in developed countries is seemingly better with the prevalence of HIV in patients with TB ranging from 9% to 25%.[16,17] However, with

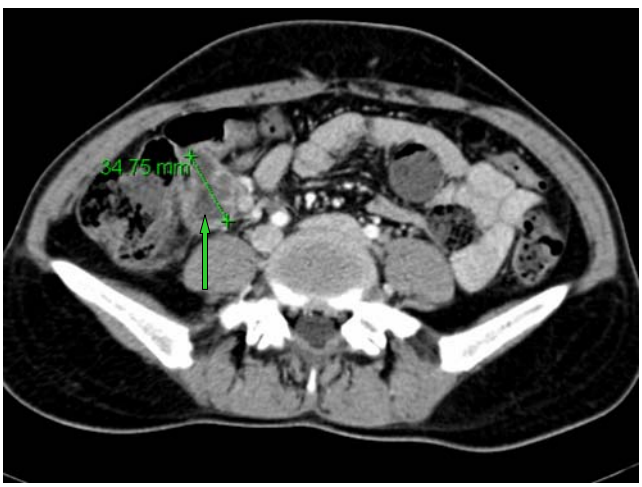

Figure 2 CT Scan showing enlarged ileocolic lymph nodes with central caseation (*arrow*).

Table 4 Area of Involvement of Abdominal Tuberculosis

Area of involvement	Number of patients (%)
Gastrointestinal	33 (57.9%)
Duodenum	2 (3.5%)
Jejunum	5 (8.8%)
Ileum	21 (36.8%)
Caecum	16 (28.1%)
Ascending colon and hepatic flexure	12 (21.1%)
Left Colon	5 (8.8%)
Anorectal region	2 (3.5%)
Mesenteric Lymph nodes	24 (42.1%)
Peritoneum	13 (22.8%)
Solid organs	
Spleen	7 (12.3%)
Liver	2 (3.5%)
Pancreas	2 (3.5%)

reporting rates of HIV status among TB patients at between 40% and 70%,[15,16] the rate of HIV infection in TB patients is likely to be much higher.

In Singapore and many developed countries, the incidence of HIV infection is increasing every year.[18] A study done early this year in Singapore on 3,000 leftover blood samples from hospitalized patients, none of whom were known to have HIV, found that one in 350 (0.3%) tested positive for HIV.[19] This has prompted one local hospital to adopt an opt-out HIV testing for all inpatients.

In developed countries, TB has become an index disease to screen for HIV. Some institutions recommend mandatory HIV testing of all TB patients in an attempt to control this deadly co-infection.[16,20] It is important to identify undiagnosed HIV patients early as effective anti-retroviral treatment is currently available, and treatment has been shown to decrease the risk of developing TB subsequently.[21]

Table 5 Types of Surgery Performed

Characteristics	Number of patients (%)
Surgery	
No surgery performed	32 (56.1%)
Surgery performed	25 (43.9%)
Type of elective surgery performed	10 (17.5%)
Laparotomy	4 3 for suspected malignancy 1 for intestinal obstruction
Laparoscopy	5
Fistulotomy	1
Type of emergency surgery performed	15 (26.3%)
Laparotomy	12 6 for perforated hollow viscus (3 Ileum, 2 right colon, 1 duodenum) 4 for intestinal obstruction 2 for suspected acute abdomen
Appendicectomy	2
Incision and Drainage of abscess	1

End-stage renal failure significantly weakens the patient's immunity, and this increases their susceptibility to develop TB as well.[22,23] Diabetes mellitus is one of the most common chronic metabolic disorders in developed countries, and it can lead to end-stage renal failure. TB must always be considered in these patients, especially in the presence of atypical signs and symptoms.

Diagnosis of abdominal TB is often difficult due to the lack of specific symptoms and pathognomonic findings.[24–27] Furthermore, its ability to mimic other inflammatory conditions[9,28] has created one of the greatest diagnostic dilemmas in modern medicine: differentiating between abdominal TB and Crohn's disease. There is much difficulty in distinguishing these two diseases as their clinical presentations, radiological features, operative findings, and even histology can be very similar. However, this step is paramount as inappropriate treatment could aggravate the underlying condition. As inflammatory bowel disease is uncommon in Singapore, anti-tuberculous medications would be started for a presumptive diagnosis of abdominal TB. In contrast, corticosteroids would be administered in the Western countries due to the prevalence of Crohn's disease.

Besides Crohn's disease, caecal malignancy has been confused with ileocaecal TB.[28,29] Both conditions can present with strictures, ulcerations, polyps, lymphadenopathy, and bowel wall thickening.[9,27] Even histological and/or microbiological confirmation may not accurately distinguish these two entities as they can coexist in the same patient.[30–32]

Gastrointestinal TB can result in significant hemorrhage.[33–36] Ulceration and erosions can occur in areas from the stomach to the rectum resulting in bleeding. Diagnosis is often obtained after endoscopic evaluation and biopsy of the affected areas. However, we did not have such a case in our series.

Mimicry of other gastrointestinal malignancies by abdominal TB is not uncommon. Two of our patients almost underwent Whipple's procedure for suspected pancreatic cancer.[37,38] Other neoplastic conditions often confused with abdominal TB included gastrointestinal stromal tumor and esophageal and liver cancer.[9,39,40]

CT scan was the most common imaging modality used in our series. Radiologic features suggestive of abdominal TB include bowel wall thickening, mesenteric lymphadenopathy, ascites, and abscess.[41,42] Although these findings are nonspecific, diagnosis of abdominal TB requires a high index of suspicion in the immuno-compromised and those with previous pulmonary TB.

The gastrointestinal tract, mesenteric lymph nodes, and peritoneum are the most common sites of involvement.[9,27,43] Terminal ileum and caecum are frequently involved within the gastrointestinal tract due to the abundance of lymphoid tissue, physiologic stasis and high rate of absorption.[27,43,44]

Surgery is aimed at achieving the diagnosis and managing the numerous complications such as perforation, bowel obstruction and hemorrhage. Studies have shown that up to 75% of these patients undergo surgery.[43–45] In our series, the corresponding figure was 43.9%. Surgery should be avoided unless absolutely necessary as many patients do poorly after surgery. There are a few reasons for this. Firstly, these patients are usually chronically ill and malnourished, making them poor surgical candidates. Secondly, the questionable or positive HIV status among these patients is another major consideration. Thirdly, appropriate therapy such as intravenous nutritional support, percutaneous drainage of abdominal collections, and empirical anti-tuberculous therapy may resolve the acute presentation, thereby avoiding surgery.[46–48]

Laparoscopy has been advocated as the ideal method in achieving definitive diagnosis in patients with suspected abdominal TB. The accuracy of achieving diagnosis of TB was reported to be over 85%.[49–51] Other than allowing direct evaluation of the peritoneum and intra-abdominal contents, laparoscopy enables the procurement of sufficient tissue for histological and microbiological examination. The advantages of laparoscopy over laparotomy include shorter hospitalization, reduced pain and analgesic usage, and better cosmetic result and may even reduce the incidence of postoperative adhesions.[52,53] However, laparoscopy should be avoided in patients with significant adhesion for risk of perforation.

Conclusion

The mode of presentation and sites of involvement of abdominal TB vary widely and are unpredictable. Although medical treatment remains the mainstay of therapy in TB, emergency surgery is still often required for its acute complications, while elective surgery may be required to resolve atypical presentations. The morbidity of surgery remains high due to the associated immuno-compromised states and its complications. The role of laparoscopy will continue to evolve and is expected to be more prominent in the management of abdominal TB.

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Laparoscopic Right Hepatectomy with Selective Vascular Exclusion

Ibrahim Dagher · Giuseppe Di Giuro · Panagiotis Lainas · Dominique Franco

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Abstract
Introduction Laparoscopic right hepatectomy remains a challenge for liver surgeons. This video illustrates, step by step, a standardized technique for laparoscopic right hepatectomy with selective vascular exclusion.
Methods The main steps of this totally laparoscopic technique are: extraparenchymal control of vascular inflow, extraparenchymal division of the right hepatic duct, complete mobilization of the right liver, control and division of the right hepatic vein, and parenchymal transection.
Results The duration of surgery was 280 min, and the blood loss was 100 ml. The postoperative period was uneventful, and the length of stay was 7 days.
Conclusion This technique has been proven to be safe and easily reproducible in hands of surgeons with expertise in both liver and laparoscopic surgery.

Keywords Laparoscopy · Right hepatectomy · Liver · Vascular control

Introduction

Laparoscopic right hepatectomy is a major vascular procedure with a substantial risk of vessel injury. We developed a totally laparoscopic technique for formal right hepatectomy with complete mobilization of the right liver and initial control of vascular inflow and outflow.[1] This strategy should minimize the risk of each surgical step.

Methods

The procedure is performed using five trocars and a 0° laparoscope. Control of vascular inflow is initially carried out. The right portal pedicle is dissected outside the liver parenchyma, and the right arterial sectorial branches as well as the right portal branch are divided. The right hepatic duct is also exposed extraparenchymally, by division of the hilar plate, and obstructed by absorbable clips before division. The right liver is then completely mobilized and separated from the anterior surface of the inferior vena cava. The right hepatic vein is gently dissected, controlled, and divided using a roticulator stapler. Parenchymal transection is easily performed on a mobilized and devascularized right liver. Transection follows the apparent demarcation line on the anterior surface of the liver, the sectioned right portal pedicle, and the inferior vena cava line. Small vessels are obstructed with thermofusion or bipolar coagulation and larger elements with absorbable clips. The hepatic stump is scrutinized for any bleeding while the level of pneumoperitoneum pressure is lowered.

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I. Dagher (✉) · G. Di Giuro · P. Lainas · D. Franco
Department of Surgery, Antoine Béclère Hospital,
157 rue de la Porte de Trivaux,
92141 Clamart cedex, France
e-mail: ibrahim.dagher@abc.aphp.fr

I. Dagher · D. Franco
Univ Paris-Sud,
Orsay 91405, France

Results

This video shows a laparoscopic formal right hepatectomy illustrating each surgical step. We have performed this procedure in 25 patients, and the indications were for tumors less than 8 cm in diameter without major vascular invasion or important subcapsular development. Two patients required conversion to open surgery (8%) due to a continuous diffuse bleeding during parenchymal transection in one patient and an anatomic variant of the portal branches in the other. Three patients suffered postoperative complications; only one was liver-specific (biliary collection treated percutaneously). There was no mortality. Surgical time was comparable to that of open surgery, while blood loss and length of stay were reduced.

Conclusions

The magnification of laparoscopy facilitates considerably the extrahepatic dissection of the right hepatic pedicle and the right hepatic vein. In selected patients, we believe that this standardized technique is appropriate and easily reproducible.

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Recurrence of Anal Adenocarcinoma After Local Excision and Adjuvant Chemoradiation Therapy: Report of a Case and Review of the Literature

Jacqueline Lee · Marvin Corman

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Abstract
Introduction Tumors arising from the anal canal are rare, comprising 1.5% of all gastrointestinal tumors in the USA. The vast majority of these anal cancers are epidermoid (cloacogenic/basaloid and squamous cell carcinomas), while adenocarcinomas reportedly occur 5% to 19% of the time. Because of its rarity, reports about anal adenocarcinoma are limited to small retrospective studies and case reports. Moreover, no series has directly compared outcomes between patients undergoing the various available treatment options, making it difficult to determine the optimal treatment for this aggressive cancer. Current management of this cancer remains controversial, with some authors believing abdominoperineal resection with permanent colostomy should be considered the standard treatment. Others propose that combined chemoradiation be adopted as a possible treatment in certain patients.
Case Presentation We describe a case of recurrent anal adenocarcinoma after conservative management with local excision and adjuvant chemoradiation therapy.

Keywords Anal adenocarcinoma · Abdominoperineal resection · Chemoradiation

Introduction

Tumors arising from the anal canal are rare, comprising 1.5% of all gastrointestinal tumors in the USA.[1] The vast majority (85%) of these anal cancers are epidermoid (cloacogenic/basaloid and squamous cell carcinomas), while adenocarcinomas reportedly occur 5% to 19% of the time.[2] The latter are more aggressive and are thought to arise from mucin-secreting stratified columnar epithelium lining the anal glands. They have their openings in the transitional zone of the anal canal and extend into the submucosa to penetrate the internal sphincter.[2] They may also be the result of distal extension of rectal adenocarcinoma.[1]

Although the pathogenesis of anal canal adenocarcinoma remains unclear, many factors have been reported to be associated with its development over the past 30 years. These include local inflammation, chronic anorectal fistulas, and Crohn's disease.[2] More recently, anal intercourse and human papillomavirus have been implicated as etiological factors.[3,4]

The presentation of anal adenocarcinoma varies depending on its anatomical location in the anus and the extent of disease. Common symptoms and findings are pain (often chronic), bleeding, pruritus ani, perianal mass, fistula, and soiling.[5] The initial presentation is often delayed because of its tendency to mimic benign anal conditions and one's low index of suspicion. Moreover, when there is an absence of mucosal involvement (as often occurs), biopsies may not be sufficiently deep to establish the diagnosis.[6] Delayed diagnosis may be a major reason why patients with anal adenocarcinoma present with more advanced disease, have a higher rate of distant metastases, and have a poorer overall survival when compared with patients with non-adenocarcinoma.[7–9]

J. Lee (✉) · M. Corman
Department of Surgical Oncology,
Stony Brook University Medical Center,
Stony Brook, NY 11794, USA
e-mail: JiLee116@gmail.com

M. Corman
e-mail: mcorman@notes.cc.sunysb.edu

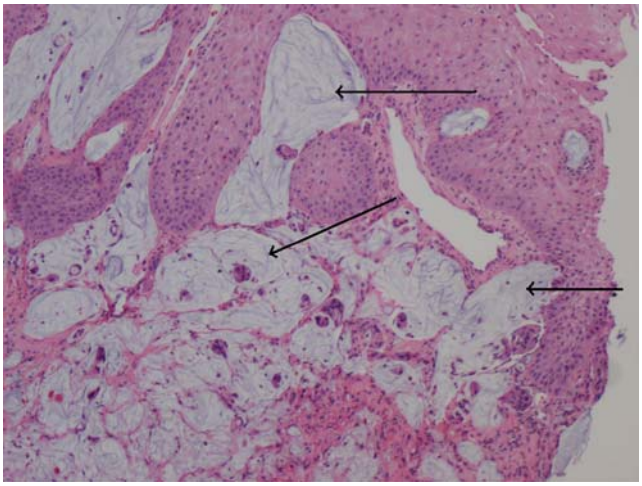

Fig. 1 Histopathological overview of adenocarcinomatous mucin pools (*arrows*) invading the overlying squamous mucosa. H&E, ×100.

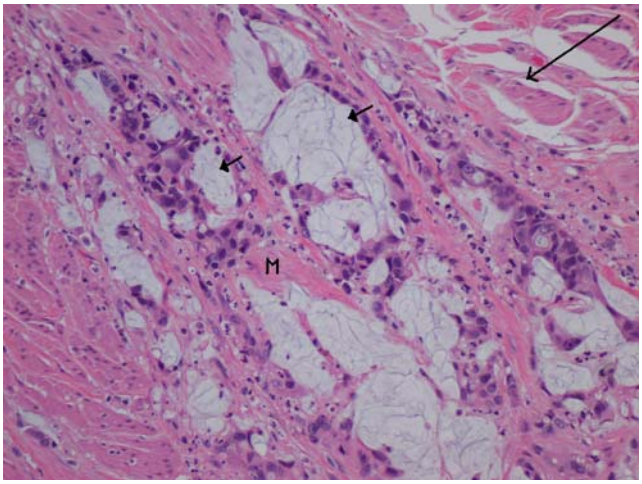

Fig. 3 Mucin pools containing neoplastic cells (*short arrows*) invading the muscularis propria (*M*). Note the striated muscle (*long arrow*) is not breached. H&E, ×200.

Case Presentation

In October 2001, a 43-year-old man presented with hemorrhoid complaints manifested by protrusion, bleeding, and the passage of mucus. He was treated by injection, ligation, and laser therapy and did reasonably well. By February 2002, the patient stated he was improved but continued to have bleeding and mucus discharge. An unusual appearing area was identified on examination, and he was advised to have a biopsy/excision. The patient did not return until later in the year, when he noticed a raised area just outside of the rectum that had been increasing in size for 6 months. There was no evidence of inguinal adenopathy. He denied any changes in bowel habits and had a negative colonoscopy in 1998. Outside of hypertension, he was generally healthy. The lesion was excised and found to be consistent with an adenocarcinoma arising in an anal duct.

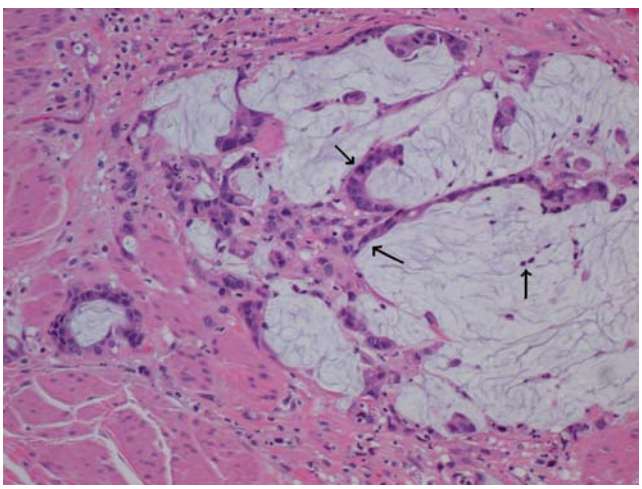

Fig. 2 Mucin pools in the muscularis propria. Neoplastic cells (*arrows*) are noted within the mucin pools. H&E, ×200.

In light of the generally poor prognosis associated with the diagnosis, abdominal perineal resection (APR) was recommended. He chose not to have the APR and subsequently underwent chemoradiation therapy. He completed the treatment regimen in February 2003 and had no evidence of residual disease. He was advised to follow up every few months but failed to pursue this regimen after negative evaluations through December 2003.

In October 2006, the patient re-presented with complaints of bleeding, discharge, and anal discomfort of several months duration. He attributed this to hemorrhoids.

Examination revealed a marginal ulcer in the posterior midline which was mildly tender and firm to palpation. There was no evidence of inguinal adenopathy. Three biopsies were taken. Histological analysis revealed mucin pools dissecting through stratified squamous epithelium as well as underlying stroma (Fig. 1). Fragments of mildly atypical glandular tissue were noted floating within the mucin pools (Fig. 2). These findings were consistent with recurrent adenocarcinoma of the anus.

The patient was admitted in December 2006 and underwent an APR. Exploration revealed no intraabdominal tumor and no evidence of peritoneal seedlings. The tumor was 3.8 cm from the anal skin margin at the anorectal junction. It extended laterally underneath the squamous epithelial lining with squamous epithelial destruction. It further extended to the muscular layer beneath the submucosa but did not breach the striated muscle. The pathologic staging of the tumor was T2N0 (Fig. 3).

The patient tolerated the procedure well and had no postoperative complications.

Table 1 Outcomes for Patients with Adenocarcinoma vs. Epidermoid Carcinoma

	Local recurrence[a] (p=0.004), %	Distant metastases[a] (p<0.001), %	5-year disease-free survival[a] (p<0.0001), %	5-year overall survival[a] (p=0.017), %
Adenocarcinoma (n=16)	54	66	19	64
Epidermoid carcinoma (n=92)	18	9	77	85

Data from Papagikos et al.[10]
[a] Five-year actuarial rate

Discussion

Because of its rarity, reports about anal adenocarcinoma are limited to small retrospective studies and case reports. Moreover, no series has directly compared outcomes between patients undergoing the various available treatment options, making it difficult to determine the optimal treatment for this aggressive cancer.

Papagikos and colleagues hypothesized that chemoradiation may replace APR as the standard initial management for anal adenocarcinoma as it does for its epidermoid counterpart.[10] They reviewed the hospital records of 16 patients with localized anal adenocarcinoma who were treated with radiotherapy with or without chemotherapy with curative intent. The treatment results for these patients were compared with those of a group of patients with epidermoid carcinoma who were all treated with definitive chemoradiation. The median follow-up was 45 months (range 5–196 months) for patients with adenocarcinoma and 44 months (range 9–115 months) for patients with epidermoid features. Although patients with epidermoid carcinoma presented with more advanced primary tumors (42% vs. 19% stage T3 or greater), both local and distant recurrence rates were significantly greater in the adenocarcinoma patients than in those with epidermoid features (Table 1). Moreover, the 5-year actuarial disease-free survival after treatment with chemoradiation was 19% in patients with adenocarcinoma compared with 77% in those with epidermoid carcinoma.[10] This study concluded that treatment with definitive chemoradiation, which had been successful with epidermoid tumors, resulted in poor local disease control rates as well as high distant recurrence rates in patients with anal adenocarcinoma. They recommended preoperative chemoradiation followed by APR to maximize pelvic disease control. Adjuvant chemotherapy may be considered to address the possibility of micrometastatic disease.[10]

In contrast, in a retrospective analysis by Joon and coworkers, six patients with localized T1 or T2N0 anal adenocarcinoma were treated with curative intent—either by chemoradiation or by radiotherapy alone.[5] After a median follow-up of 6.6 years, none developed local or distant recurrence. All except one were alive and free of disease. Their study concluded that chemoradiation appeared to be the preferred primary modality of treatment for early-staged anal adenocarcinoma because it controlled the tumor while maintaining anorectal function. APR was recommended to be reserved for persistent or recurrent disease.[5]

Belkacemi and associates conducted one of the few large retrospective studies on primary anal adenocarcinoma.[2] This involved 82 patients with tumors staged T1 to T4. The

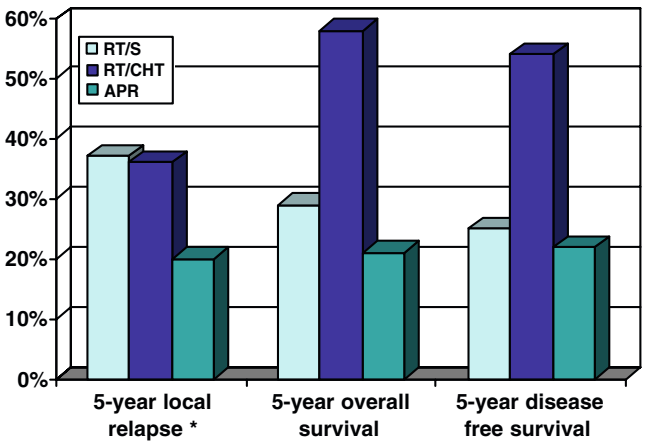

Fig. 4 Five-year local relapse, overall survival, and disease-free survival rates. *Asterisk* Not statistically significant. Data from Belkacemi et al.[2]

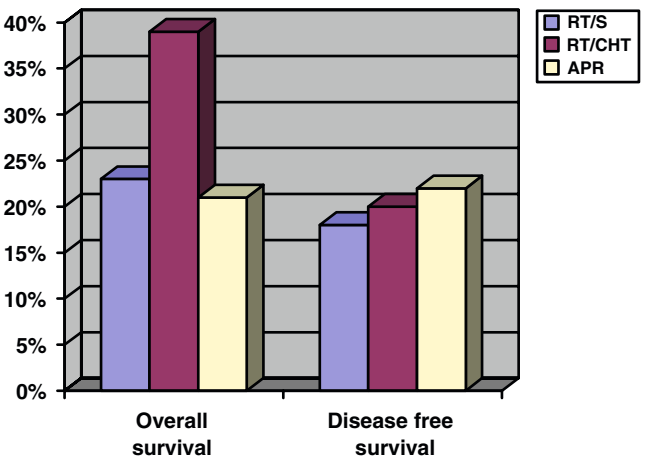

Fig. 5 Ten-year overall survival and disease-free survival rates. Data from Belkacemi et al.[2]

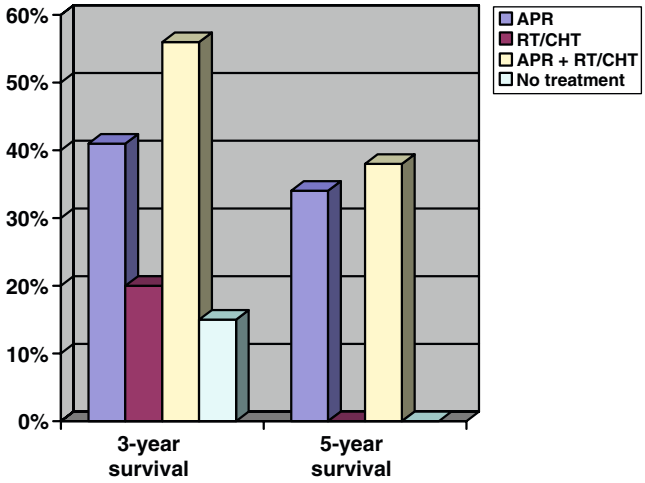

Fig. 6 Three- and five-year survival rates. Data from Li et al.[11]

patients were separated into and analyzed according to three treatment approaches: radiotherapy/surgery, combined chemoradiotherapy (RT/CHT), and APR alone. The main patient characteristics were distributed evenly among the three treatment groups. The authors concluded that primary adenocarcinoma of the anal canal requires rigorous management, with better survival rates achieved after combined RT/CHT (5-year overall and disease-free survival rates of 58% and 54%, respectively, Fig. 4). Similar results were seen at the 10-year mark, though disease-free survival was slightly lower in patients treated with RT/CHT compared with patients who underwent an APR (20% vs. 22%, respectively; Fig. 5). APR was recommended only for salvage treatment. A multivariate analysis showed that T and N stage, histologic grade, and treatment modality were independent prognostic factors for survival.[2]

In contrast, a retrospective study was reported by Li and coworkers involving 49 patients with adenocarcinoma of the anal canal.[11] They found that APR with adjuvant chemoradiation was the preferred principal treatment (Fig. 6). The 5-year survival rates in patients with APR alone, chemoradiation therapy, APR with adjuvant chemoradiation, and without any treatment were 34.4%, 0%, 37.5%, and 0%, respectively.

Table 2 Outcome Data for Patients Undergoing Different Treatments for Anal Adenocarcinoma

	Local control rate (%)	No evidence of disease[a] (%)
APR with RT or RT/CHT (pre- and/or post-operative), *n*=8	63	37.5
LE with adjuvant RT or RT/CHT, *n*=5	60	20

Data from Beal et al.[12]
APR Abdominoperineal resection, *RT* radiotherapy, *RT/CHT* combined chemoradiotherapy, *LE* local excision
[a] No evidence of disease at end of follow-up period

Table 3 Summary of Current Recommendations

	n	Pathology (anal adenocarcinoma)	Recommendations
Papagikos et al.	16	Localized T1-T4, N0-N3	Neoadjuvant RT/CHT + APR
Joon et al.	6	Localized T1-T2N0	RT/CHT
Belkacemi et al.	82	T1-T4, N0-N3, M1	RT/CHT
Li et al.	49	T1-T4, N0-N3, M1	APR + adjuvant RT/CHT
Beal et al.	13	Localized T1-T4, N0-N2	APR + RT/CHT (pre- or post-op)

n Sample size, *APR* abdominoperineal resection, *RT/CHT* combined chemoradiotherapy

At Memorial Sloan-Kettering Cancer Center, 13 patients with primary anal adenocarcinoma were followed for a median of 19 months after treatment with either neoadjuvant RT/CHT and APR, local excision followed by postoperative radiation alone or RT/CHT, or APR with adjuvant RT/CHT (Table 2).[12]

From this limited study, the authors concluded that the combination of APR and combined modality therapy (whether it be neoadjuvant or adjuvant) is a reasonable approach for the treatment of this rare tumor.

Table 3 summarizes the overall recommendations from the studies mentioned above.

Conclusion

Though there is currently no standard protocol for the treatment of primary anal adenocarcinoma, APR is increasingly used with combined modality treatment. Nevertheless, anecdotal success has been reported with local excision and chemoradiation treatment for selected patients with early-stage anal adenocarcinoma. Larger studies to date have shown patients with anal adenocarcinoma treated with chemoradiation, with or without local excision, seem prone to more systemic metastases and hence have a reduced disease-free survival. Therefore, more studies recommend APR with chemoradiation as the preferred treatment for this rare cancer. In contrast, chemoradiation treatment alone had superior outcomes in patients with squamous cell carcinoma. The presented case is an example of local recurrence after treatment by local excision and chemoradiation, with subsequent APR needed for salvage treatment. Clearly, close follow-up is necessary if one elects to embark on local excision, irrespective of the addition of RT/CHT. APR has been necessary in most patients for local

control, with the definitive role of neoadjuvant or adjuvant combined chemoradiation therapy not yet defined.

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Efficacy of the Electrothermal Bipolar Vessel Sealer in Laparoscopic Spleen-Preserving Distal Pancreatectomy with Conservation of the Splenic Artery and Vein

O. Suzuki · E. Tanaka · S. Hirano · M. Suzuoki · H. Hashida · T. Ichimura · N. Sagawa · T. Shichinohe · S. Kondo

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Abstract
Introduction Laparoscopic spleen-preserving distal pancreatectomy (LSPDP) with conservation of the splenic artery and vein has recently been performed as a minimally invasive surgery to retain splenic function in the treatment of pancreatic diseases. As the branches of the splenic vessels are very delicate, division of these branches increases the risk of bleeding.
Materials and Methods To overcome this problem, we have used the electrothermal bipolar vessel sealer (EBVS) to divide branches of the splenic vessels in LSPDP while conserving the splenic vessels themselves.
Results The EBVS reliably provided excellent and safe hemostasis, minimizing the risk of serious blood loss.
Conclusion Use of the EBVS is safe and efficient in LSPDP with conservation of the splenic vessels.

Keywords Laparoscopy · Distal pancreatectomy · Spleen-preserving · Electrothermal bipolar vessel sealer

Introduction

Various laparoscopic surgeries are in current use as effective options for the treatment of pancreatic diseases[1] and advances in diagnostic imaging have facilitated the diagnosis of cystic lesions and endocrine tumors in the distal pancreas.[2,3] Given their benign nature or low-grade malignant potential, minimally invasive surgeries to preserve organic function are desirable approaches to treating these lesions. Among these surgical procedures, laparoscopic spleen-preserving distal pancreatectomy (LSPDP) with conservation of the splenic artery and vein has seen increasing in practice.[1–4] This laparoscopic surgery requires sufficient surgical skills to overcome the difficulties inherent in safely and securely dividing branches of the splenic vessels as these branches are very fine.

The electrothermal bipolar vessel sealer (EBVS) achieves excellent hemostasis by securely sealing tissue and vessels. The efficacy of this system for dividing splenic and colonic vessels in various laparoscopic surgeries has been documented.[5,6] However, few studies have reported the use of the EBVS to reliably divide branches of a vessel while providing effective hemostasis in an attempt to preserve the vessel.[1] Moreover, no reports have provided detailed surgical procedures for laparoscopic pancreatic resection using the EBVS. We, therefore, describe herein our surgical procedures for using the EBVS in LSPDP with conservation of the splenic vessels during the treatment of distal pancreatic tumors. The EBVS was particularly useful in reliably dividing branches of a vessel while providing safe and efficient hemostasis, with the specific aim of preserving the pivotal vessel.

Material and Methods

We divided the gastrocolic ligament using the electrothermal bipolar vessel sealer (EBVS; LigaSure™ V, Valleylab, Boulder, CO, USA) with a shaft diameter of 5 mm to enter

O. Suzuki (✉) · E. Tanaka · S. Hirano · M. Suzuoki · H. Hashida · T. Ichimura · N. Sagawa · T. Shichinohe · S. Kondo
Department of Surgical Oncology,
Hokkaido University Graduate School of Medicine,
N-15, W-7, Kita-ku,
Sapporo, Hokkaido 060-8648, Japan
e-mail: onsuzuki@tkeijinkai.gr.jp

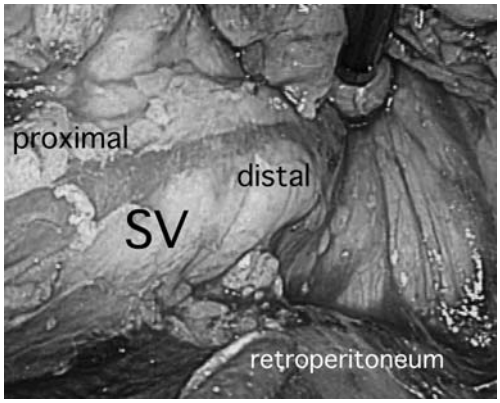

Figure 1 The pancreatic body was mobilized from the retroperitoneum until the splenic vein (*SV*) could be visualized.

the bursa omentalis. After identifying the pancreatic tumor and confirming its location on intraoperative laparoscopic ultrasonography, we determined the level of division of the pancreas. At the superior pancreatic border, we cut the peritoneum, exposing and taping the splenic artery. At the inferior margin of the pancreatic body, we incised the retroperitoneum from medially to laterally. Along the line of division of the retroperitoneum, we bluntly and sharply mobilized the pancreatic body from the posterior parietal retroperitoneum until the splenic vein could be visualized (Fig. 1).

We cut the fusion fascia of Toldt[7] covering the splenic vein in the vicinity of the level of division of the pancreas, exposing the splenic vein. Paying close attention to avoid damaging branches, we carefully dissected and taped the splenic vein using right-angle Kelly forceps. Applying slight caudal tension to the tape, we could easily and safely identify the branches of the vessel. We bluntly and partially dissected branches running just deep to the pancreas (Fig. 2a). As isolation of these branches might cause a vascular tear and troublesome bleeding, we did not isolate branches with surgical devices. To position the entire branch and the pancreatic parenchyma between the jaws of the EBVS, we inserted the jaws into the parenchyma. We, then, securely sealed and divided the entire branch along with the neighboring parenchyma (Fig. 2b). This completely freed the splenic vein from the pancreas by dividing the branches and, in effect, dissecting out the splenic vein, allowing insertion of the blade of a linear stapler between the pancreas and splenic vein. This same procedure was repeated for the splenic artery. At the level of division of the pancreas, we transected the pancreas using the linear stapler. Pulling the distal pancreas ventrally allowed us to readily identify the distal splenic vein under only slight tension. At the lateral and ventral margins and longitudinally along the splenic vein, we clamped the branches and surrounding pancreatic parenchyma between the jaws of the EBVS. We, then, sealed and divided branches along with the pancreas, applying the entire length of the jaws (Fig. 3). This procedure was carefully and gently performed almost to the splenic hilum. Next, we pulled the distal pancreas laterally and ventrally. Taking care not to injure the adventitia of the splenic artery, we sealed and divided the branches supplying the pancreas using the EBVS. This procedure was employed longitudinally along the splenic artery towards the splenic hilum without dissection and isolation. After confirming the distal margin of the pancreas, we resected the distal pancreatic tissue (Fig. 4).

Results

A 72-year-old woman was brought unconscious to her family doctor. Laboratory tests identified marked hypoglycemia and hyperinsulinemia, and level of consciousness improved immediately upon administration of glucose.

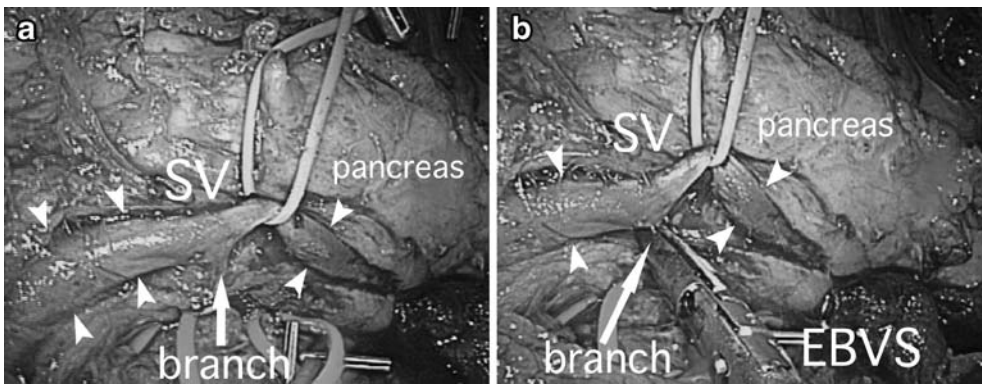

Figure 2 **a** By applying tension to the tape, the *branch* of the splenic vein (*SV*) running to the *pancreas* was easily identified and partially dissected. *Arrowhead*: the edge of the splenic vein. **b** Positioning the entire branch of the splenic vein (*SV*) and the pancreatic parenchyma between the two jaws of the electrothermal bipolar vessel sealer (*EBVS*), the jaws were inserted into the parenchyma. The *branch* was securely sealed and divided with the neighboring parenchyma. *Arrowhead*: the edge of the splenic vein.

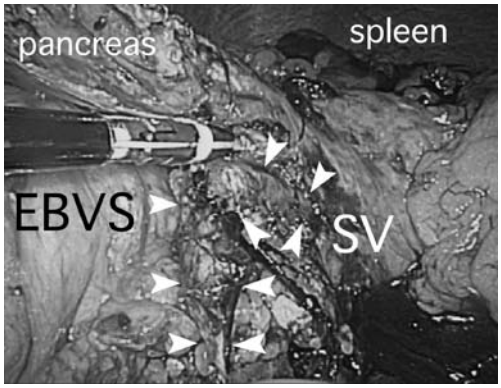

Figure 3 Branches of the splenic vein (*SV*) and the surrounding pancreatic parenchyma were clamped between the jaws of the electrothermal bipolar vessel sealer (*EBVS*). Branches along with the pancreas were sealed and divided, applying the entire length of the jaws. *Arrowhead*: the edge of the splenic vein.

Abdominal computed tomography showed a 1-cm enhanced tumorous lesion in the distal pancreas. The patient was diagnosed with insulinoma. Simultaneously, she found dysfunctional uterine bleeding, diagnosed with advanced uterus cancer, and received radiochemotherapy, which resulted in the control of the uterine bleeding. In addition, she had a previous history of bilateral knee osteoarthritis, which compelled her to walk with a stick. LSPDP with conservation of the splenic vessels was scheduled. As the tumor located too close to the main pancreatic duct, we did not choose the enucleation. Surgery was completed without any notable complications. Operative time was 344 min, and blood loss was 120 ml. The postoperative course was uneventful. She resumed oral intake on postoperative day 2 and was discharged on postoperative day 10. As of 6 months postoperatively, no episodes of hypoglycemia had occurred. Pathology revealed well-differentiated insulinoma.

Discussion

The laparoscopic approach should be encouraged to treat benign lesions or borderline malignancy in the distal pancreas; then, a variety of laparoscopic options including laparoscopic distal pancreatectomy with splenectomy (LDP), LSPDP, and laparoscopic enucleation of pancreatic tumor have been introduced as a minimally invasive surgery.[1–4]

LDP has been commonly performed because splenectomy with distal pancreatectomy could simplify the operative technique same as a conventional open manner. Recently, LSPDP has been advocated on the concept of organic function-preservation. However, the question whether surgeons should preserve the spleen still remains controversial.[8,9] Multiple concerns including technical difficulties, prolonged operative time, and increased intraoperative blood loss from small venous tributaries continued to be raised as barriers to LSPDP. In contrast, for an attempt to prevent potential complications following splenectomy, such as thrombosis, infection, and immunosuppression, spleen-preserving surgery is being performed in selected patients[2,4,7] and could affect survival for patients with cancerous diseases.[10]

Laparoscopic enucleation of pancreatic tumor (LE) is the procedure of choice to resect benign tumors located on the anterior surface of the distal pancreas. However, the patients with tumors close to the main pancreatic duct (MPD) had better be managed by LSPDP or LDP instead of LE, as the MPD might be easily damaged in LE.

LSPDP can be achieved in two ways: (1) dividing the splenic vessels with the left gastroepiploic and short gastric vessels preserved, on which subsequent splenic blood flow might rely; or (2) preserving the splenic vessels.[11] With the first technique, the surgeon must keep in mind that blood supply to the spleen may be insufficient after division of the splenic artery, resulting in complications such as splenic infarction and abscess formation.[1–3] With the second technique, branches of the splenic vessels must be divided from the pancreas in order to preserve the ability of the splenic artery to supply sufficient blood flow to the spleen postoperatively. The splenic vessels are hemicircumferentially surrounded by pancreatic parenchyma, and branches of the splenic vessels are very fine and easily damaged. To obtain adequate blood flow to the spleen, this procedure mandates sophisticated, careful, and gentle tissue handling with high-level expertise.

In LSPDP with conservation of the splenic vessels, surgical instruments such as electrocautery, laparoscopic coagulating shears (LCS), EBVS, and clips are often employed to control splenic vessels. Few studies have reported the effectiveness of these surgical devices for handling splenic vessels in this laparoscopic surgery.[4] Electrocautery is useful for cutting the peritoneum covering the vessels, but the bleeding from the small vessel is difficult to control even with bipolar electrocautery. When

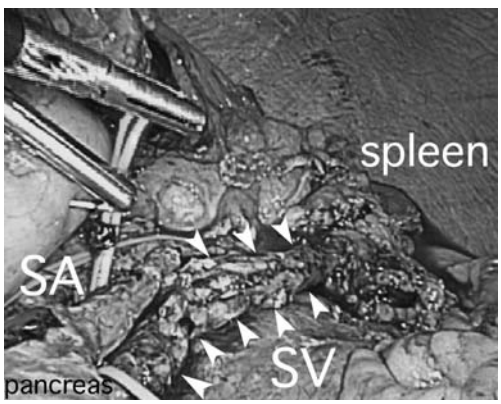

Figure 4 After resection of the distal pancreatic tissue, the splenic artery (*SA*) and vein (*SV*) were completely preserved. *Arrowhead*: the edge of the splenic vein.

using LCS, the small vessels could be securely sealed by sufficient dissection and isolation; however, mandatory insertion of a tissue pad behind the extremely delicate branches of the splenic vein might be challenging. Insufficient sealing of the LCS might cause the troublesome bleeding. Clipping of the small splenic vessels needs also securely to dissect and isolate the vessels. Dislodgement of clips might cause massive bleeding, and hamper stapling for division of the pancreas.

In contrast, the EBVS is an effective instrument for sealing and dividing minor vessels, specifically without prerequisite dissection or isolation. In particular, in our technique for LSPDP, use of the EBVS can be divided into phases before and after transection of the pancreas, as follows: First, the extent of dissection should be limited to exposing branches of the splenic vein on the dorsal surface of the pancreas, and isolation of branches is never intended (Fig. 2a). The tips of the jaws are inserted into the pancreatic parenchyma to seal and divide the entire branch with surrounding parenchymal tissue (Fig. 2b). Repetition of these procedures facilitates dissection of the splenic vein and safe detachment from the pancreas, allowing pancreatic transection. Second, slight tension on the splenic vein by tugging on the distal pancreas allows easy identification of the splenic vein. Forceful procedures for dissecting and isolating branches should be studiously avoided. Along the lateral margins of the splenic vein, the entire length of the EBVS jaws is applied to securely clamp the parenchyma and venous branches (Fig. 3). The same technique is extremely useful for sealing and dividing the branches of the splenic artery.

In the present case, LSPDP was chosen as a procedure of choice because the pancreatic tumor located at the tail close to the MPD, and splenic salvage could have benefited the prognosis of malignancy. With the use of the EBVS, we successfully performed LSPDP without any complications.

Conclusion

Using the EBVS in LSPDP allows division of the splenic vessels with secure hemostasis. Surgery with the use of the EBVS is safe and effective in laparoscopic pancreatic resection requiring vessel preservation, such as LSPDP with conservation of the splenic vessels.

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Transumbilical Gelport Access Technique for Performing Single Incision Laparoscopic Surgery (SILS)

Aziz M. Merchant · Michael W. Cook · Brent C. White · S. Scott Davis · John F. Sweeney · Edward Lin

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Abstract
Introduction Single incision laparoscopic surgery (SILS) is an area of active research within general surgery.
Discussion A number of procedures, including cholecystectomy, appendectomy, urologic procedures, adrenalectomy, and bariatric procedures, are currently being performed with this methodology. There is, as yet, no standard published technique for single-port access to the peritoneal cavity for SILS. We describe, herein, an access technique utilizing existing instrumentation including a Gelport and wound retractor that is reliable and easy. This technique has been used successfully at our institution for a number of single incision laparoscopic procedures.

Keywords Single incision laparoscopic surgery · Gelport · Single-port access

Introduction

Single incision laparoscopic surgery (SILS), also known as laparoendoscopic single-site surgery or single-port access surgery, is an area of active investigation for abdominal surgery. A number of advantages have been proposed including cosmesis (scarless abdominal surgery performed through an umbilical incision), less incisional pain, and the ability to convert to standard multiport laparoscopic surgery if needed. Single incision cholecystectomy[1] has been described by Piskun et al., as early as 1999 with the insertion of two trocars through the umbilical incision and additional stay sutures to stabilize the gallbladder. In addition, a number of recent reports of single-incision donor nephrectomies[2,3] and other urologic applications[4,5] have been described, as well as single incision sleeve gastrectomies for morbid obesity.[6]

The primary disadvantages of SILS are the restricted degrees of freedom of movement, the number of ports that that can be used, and the proximity of the instruments to each other during the operation—all of which increase the complexity and technical challenges of the operation. Many of these difficulties can be related to the technique of port placement and utilization during single incision laparoscopic surgery. A number of methods have been described for port access to perform SILS, including multiple fascial punctures through one skin incision, the use of additional transabdominal sutures to stabilize the target organ, and use of novel port access devices such as the Unix-X™ (Pnavel Systems, Brooklyn, NY, USA)[7] and R-port™ (Advanced Surgical Concepts, Wicklow, Ireland).[3] To further overcome the technical challenges for SILS, different instruments that provide angulations and small profile trocars are being developed.

We describe our method of establishing single-port access for SILS that has reduced some of the technical challenges of performing SILS cholecystectomies. Our method involves the use of existing instrumentation, including a wound protector and the Gelport (Applied Medical, Rancho Santa Margarita, CA, USA). In addition, the use of the Gelport allows introduction of three to five

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A. M. Merchant · M. W. Cook · B. C. White · S. S. Davis · J. F. Sweeney · E. Lin (✉)
Emory Endosurgery Unit, Department of Surgery,
Emory University,
1364 Clifton Road, Suite H-127,
Atlanta, GA 30322, USA
e-mail: elin2@emory.edu

ports for operation, with minimal "clashing" of ports and instruments during the procedures.

Surgical Technique

After induction of general anesthesia and prepping and draping the patient, we first prepare the Gelport device to minimize leakage of pneumoperitoneum during the procedure. This is accomplished by layering several sheets of Ioban (3M, St. Paul, MN, USA) on the undersurface of the Gelport and cutting them to appropriate circular dimension (Fig. 1).

A 1-cm umbilical skin incision is made and carried down to the peritoneum. The Gelport's double-ring wound retractor (Alexis®, Applied Medical, Rancho Santa Margarita, CA, USA) is inserted through the incision, which stretches the fascial diameter to 1.5 cm (Fig. 2). A 5- or 10-mm trocar is inserted through the Gelport centrally, and the Gelport with trocar is latched on to the wound retractor ring. It is easier to insert the first trocar through the Gelport, prior to securing the Gelport to the wound protector. Pneumoperitoneum is established and a 10-mm 30° videoscope inserted. Two 5-mm operating ports are inserted in 2- and 8-o'clock positions, with the videoscope port as the center. Graspers and dissectors are inserted through these accessory ports as needed to assist in the gallbladder dissection (Fig. 3). This system allows the insertion of an additional 5-mm trocar anytime during the operation, as well as the insertion of an instrument directly through the Gelport without the use of a trocar. The videoscope can also be placed through the other ports for different viewing perspectives and not be permanently fixed in the center. The Gelport system essentially creates trocar positions with "flexible fulcrums" that allow combined motions in linear, radial, and translational planes (Fig. 4).

A cholecystectomy is then performed in standard fashion. The gallbladder is extracted from the abdomen through the single incision, and the wound retractor allows the extraction to be achieved easily as the fascial diameter is already enlarged. The single fascial incision is closed, followed by skin closure (Fig. 5).

In summary, a transumbilical fascial incision 1 to 1.5 cm in length is made, and a wound protector is inserted. A Gelport is then snapped on to the wound protector. Pneumoperitoneum is sealed within this Gelport/wound protector system. Videoscopes and instruments are inserted through trocars placed through the Gelport, traveling through the protected fascial wound and into the abdomen.

Comment

SILS has been performed since the late 1990s for a wide variety of surgical procedures. As early as 1998, a single incision laparoscopic appendectomy[8] was described, in which the appendix was mobilized laparoscopically and the appendectomy was performed extracorporeally through the single umbilical incision. This was followed by reports in the urologic literature of single incision surgery for various procedures.[2,3] Recently, we and others have performed single incision laparoscopic colorectal surgery,[7] adrenalectomy,[4,5] and cholecystectomy.[1,9] In addition, bariatric procedures such as laparoscopic sleeve gastrectomies and gastric band placements have been performed using the SILS method.[6] Single-port thoracoscopic procedures for evacuation of empyema had also been described.[10]

Critics of SILS cite the lack of data regarding patient benefit over standard open or multiport laparoscopic techniques. The potential need for advanced instrumentation may translate into increased costs as well. In addition, the lack of triangulation, pneumoperitoneum leaks, and instrument "clashing" have been described as real disadvantages of this procedure, thereby increasing difficulty.

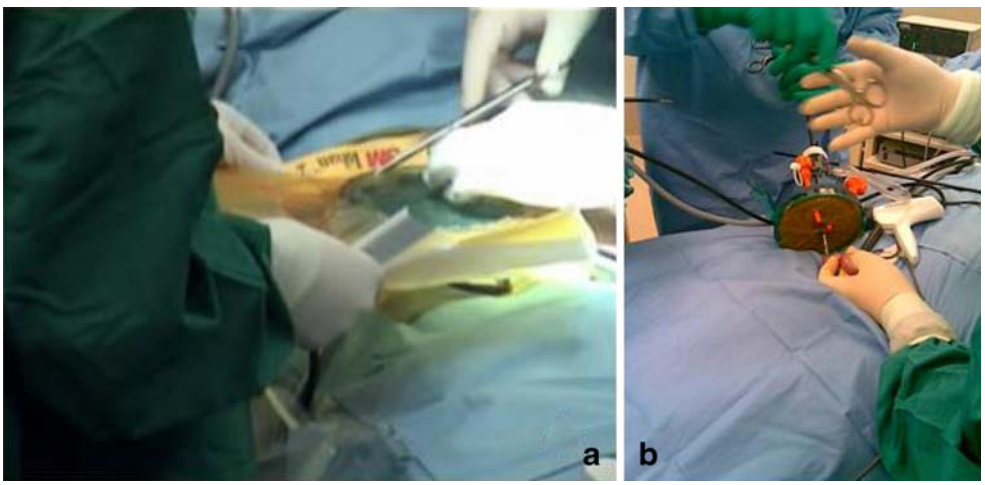

Figure 1 **a**, **b** A large Ioban is used multiple times to coat the undersurface of the Gelport device. This helps prevent leakage of pneumoperitoneum throughout the case, as additional trocars are punctured through.

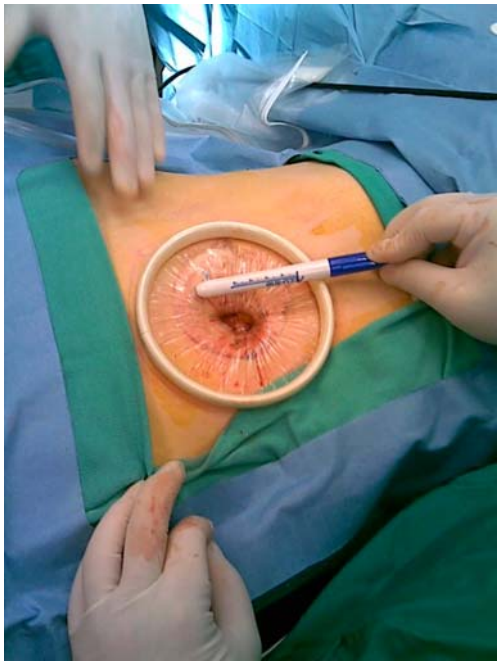

Figure 2 After the fascia is incised, an Alexis® wound retractor is inserted. The wound retractor allows stretching of the fascial incision to about 1.5 cm and for easy access with instruments into the abdominal cavity.

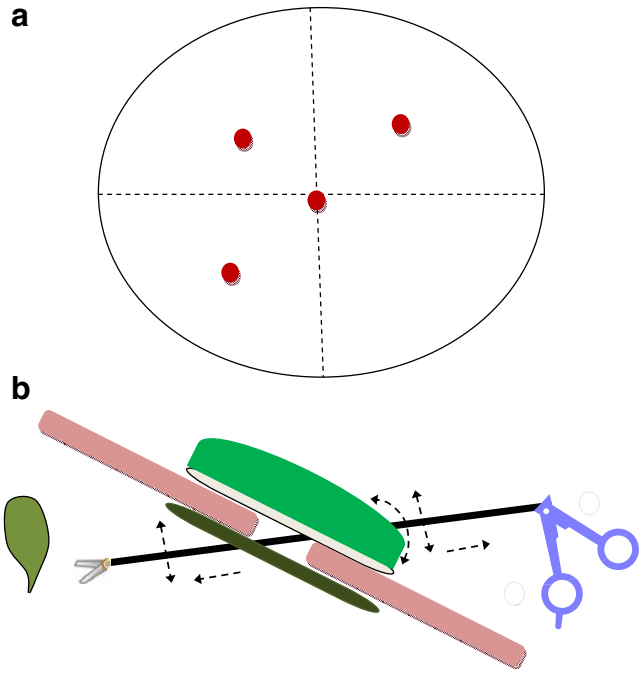

Figure 4 **a** Initial trocar placements, one in each quadrant of the Gelport surface. **b** The "flexible fulcrum" allows movement in linear, radial, and translational planes.

There is no standard technique for trocar placement in SILS. The first reports of laparoscopic cholecystectomy, from 1999,[1] and current reports[9] used multiple fascial punctures from a single umbilical skin incision to insert multiple ports for operation. The development of skin flaps circumferentially to accommodate the subcutaneous ports is necessary with the multiple fascial puncture technique. The theoretical disadvantages of this technique include the potential weakening of fascia by intentionally creating a "Swiss cheese" defect. Furthermore, seroma formation after skin flap elevation is a common occurrence. Other reports include the use of specialized newly developed umbilical port entry systems, such as Unix-X^{TM} [7] and R-port^{TM} [3] for

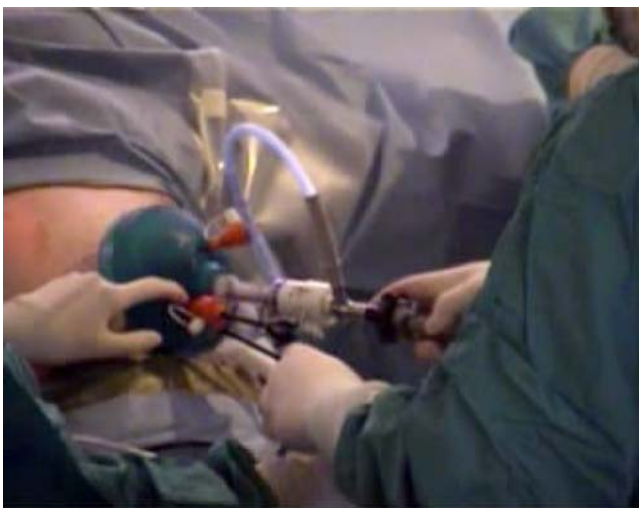

Figure 3 The Ioban-sealed Gelport is snapped on with the first trocar pre-inserted. After insufflation, the central trocar of the "flexible fulcrum" can be a 5- or 10-mm videoscope, with the operating ports started off in a 2- and 8-o'clock position.

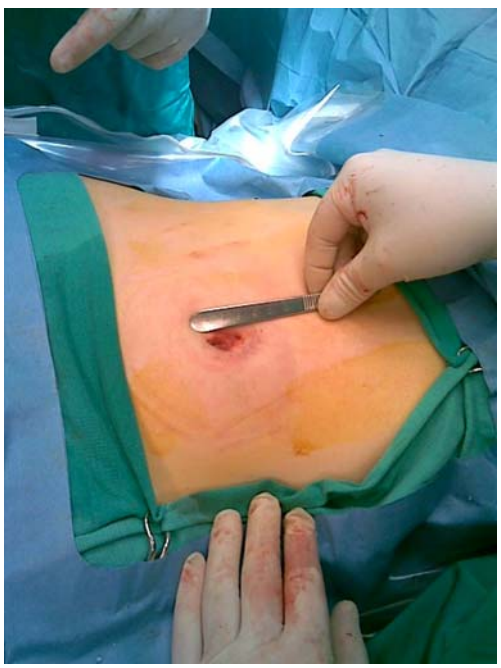

Figure 5 This figure illustrates the size of the incision used and appearance after closure of the umbilical wound.

access. The above methods also result in placement of ports that are too close to each other for effective hand movements. In addition, the use of "suture slings" to aid in retraction and exposure of the target organ, such as in appendectomy[11] or cholecystectomy,[9] has been described. This requires additional punctures through the abdominal wall to establish the sling.

Our Gelport technique overcomes some of the disadvantages of current techniques. We use one transumbilical incision with a wound retractor/protector that increases the size of the incision. The Gelport and wound protector are ubiquitous devices that are commonly employed for hand-assisted abdominal surgeries. In addition, the Gelport provides a "flexible fulcrum" for insertion and manipulation of a videoscope and up to three or four 5-mm trocars with minimal clashing of instruments, while minimizing the loss of degrees of freedom for operation. In our practice, we generally avoid the use of additional puncture wounds for suture slings, as there is enough access to provide the appropriate retraction of the target organ. Lastly, the Gelport technique readily maintains the pneumoperitoneum.

Our current experience with the SILS Gelport access system includes 21 cholecystectomies. In addition, we have performed laparoscopic hemicolectomies, a laparoscopic adjustable gastric band placement, a laparoscopic sleeve gastrectomy, and laparoscopic esophagectomy. Our longest follow-up is approximately 6 months. The major complaint from patients is pain from the umbilical wound site. At follow-up, there have been no wound complications such as surgical site infections or hernias. Our cholecystectomy and gastric band patients have all left on the same day of surgery with minimal narcotic requirement. Operative times for SILS cholecystectomy have ranged from 45 to 90 min. Two cases were performed for acute cholecystitis, one of them requiring the addition of an accessory port in the right upper quadrant for dissection. SILS cholecystectomy performed for acute cholecystitis proved to be slightly more challenging, requiring longer operative times.

In summary, we provide an alternative access system using a commonly used Gelport device with a flexible fulcrum to allow single-port access surgery to be performed. According to our experience, wide variety of laparoscopic procedures, patient populations, and disease processes are amenable to this approach. We believe that this type of port access is one way to lessen the technical difficulties of performing SILS and therefore broaden its applicability to other procedures.

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Prevention and Management of Pancreatic Fistula

Mark P. Callery · Wande B. Pratt · Charles M. Vollmer Jr

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Abstract Despite significant improvements in the safety and efficacy of pancreatic surgery, post-operative pancreatic fistulae remain an unsolved dilemma. These occur when the transected pancreatic gland, pancreatic-enteric anastomosis, or both, leak rendering the patient at significant risk. They are especially important today since indications for resection (IPMN, carcinoma) continue to increase. This review considers definitions and classifications of pancreatic fistulae, risk factors, preventative approaches and offers management strategies for when they do occur. Key citations from the past seventeen years have been scrutinized, and together with personal experience, provide the basis for this review.

Keywords Pancreatic fistula · ISGPF · Pancreatic resection · Whipple · Distal pancreatectomy · Octreotide · Risk factor

In recent years, the field of pancreatic surgery has achieved considerable advancements in the management of periampullary neoplasms, pancreatitis, cystic and neuroendocrine lesions. Refinements in operative technique and improvements in postoperative care have gradually contributed to declines in operative mortality, shorter hospital stays, and better quality of life. However, postoperative complications, primarily, pancreatic fistula, abscess, and delayed gastric emptying, still occur with 30–60% frequency, and often result in catastrophic events such as hemorrhage, intrabdominal sepsis, or multi–system organ failure.[1–2] The consequences of these adverse events include increased utilization of intensive care facilities and resources, prolonged hospital stays, higher reoperative and readmission rates, and, ultimately, greater hospital costs.

Among all postoperative complications, pancreatic fistula is widely considered to be the most troublesome and uncompromising in pancreatic surgery. It is the factor most often linked with operative death, longer hospital stays, and increased hospital costs.[3] Recent reports indicate that pancreatic fistula occurs in 5–30% of cases; yet, even in experienced hands, this rate has not declined significantly in the previous three decades.[4] Hence, there has been considerable interest in understanding the clinical effects of this ominous complication and identifying new methods to prevent its occurrence. This article will explore these concepts and offer specific perioperative management approaches to mitigate the impact of clinically relevant pancreatic fistula. Studies published during the previous two decades (January 1990 to November 2007) were scrutinized to accomplish these objectives.

M. P. Callery (✉) · W. B. Pratt · C. M. Vollmer Jr
Department of Surgery, Beth Israel Deaconess Medical Center,
Harvard Medical School,
330 Brookline Avenue, St. 9,
Boston, MA 02215, USA
e-mail: mcallery@bidmc.harvard.edu

Definitions of Pancreatic Fistula

The focal point of any discussion of pancreatic fistula is its definition. Numerous and widely varying definitions of pancreatic fistula have emerged in the recent literature, but none provides a simple and reliable system for describing the fluid collections and abscesses which arise from the pancreas.

The challenge is multi-factorial, and first requires the use of correct terminology. The term *fistula* refers to an abnormal communication (congenital, pathologic, or surgically created) from one epithelialized surface to another. It differs from *leakage*, which is an abnormal escape of fluid through an orifice or opening.[5] These terms are used interchangeably in pancreatic surgery, and it is nearly

impossible to find consensus in the literature, even among specialty-trained pancreatic surgeons. The truth probably lies somewhere in between: either a failure of the pancreatic–enteric anastomosis or leakage of pancreatic juice from the transected pancreatic surface.

Factors underlying the development of pancreatic fistulae have been rigorously scrutinized in prior studies. Exocrine output from the pancreatic remnant is now widely implicated as the causative factor of pancreatic fistula, and it has long been appreciated that leakage of amylase-rich fluid is a defining characteristic. Most definitions of fistula rely on amylase content from an intra-abdominal drain, as well as the daily volume of effluent. Yet, in the past decade, there has been considerable debate as to what thresholds define a pancreatic fistula. In a recent study, Bassi et al. examined 26 definitions of pancreatic fistula published between 1991 and 2000.[6] Each definition was arbitrarily assigned a score based on daily fluid output criteria and the timing of fistula development (i.e., number of days from the onset and/or duration of fistula). From this analysis, four definitions were formulated to summarize concepts of pancreatic fistula: (1) fluid output more than 10 ml/day of amylase-rich fluid since the fifth postoperative day or for more than 5 days; (2) fluid output more than 10 ml/day of amylase-rich fluid since the eighth postoperative day or for more than 8 days; (3) fluid output between 25 and 100 ml/day of amylase-rich fluid since the eighth postoperative day or for more than 8 days; and (4) fluid output more than 50 ml/day of amylase-rich fluid since the 11th postoperative day or for more than 11 days. These definitions were then applied to a group of 242 patients who underwent pancreatic resection with pancreaticojejunal anastomotic reconstruction. The authors determined the incidence of pancreatic fistula in the same cohort of patients ranged from 9.9% to 28.5%, depending on the defining criteria (Table 1). This variance illustrates the problem of using different definitions of fistula, and has the potential to obfuscate comparisons of techniques and outcomes in pancreatic surgery.

The issue is further compounded by the concept of "clinical relevance", a phrase often employed to distinguish asymptomatic, biochemical pancreatic fistulae from those that are associated with clinical illness, therapeutic intervention, or death. In 1997, Lowy et al. were among the first to describe this concept, using a definition of *clinical pancreatic fistula* to refer to drainage of amylase-rich fluid in association with fever, leukocytosis, sepsis, or the need for percutaneous drainage; a *biochemical pancreatic fistula* was used to describe an elevated drain amylase level on or after postoperative day three that was asymptomatic and resolved spontaneously.[7] These definitions have been adopted and modified by many investigators, most notably the International Study Group on Pancreatic Fistula (ISGPF), a group of 37 notable pancreatic surgeons from 15 countries, who met during the International Postgraduate Course "HPB Marathon" in Athens, Greece, to review the literature and discuss their experiences with pancreatic fistula.

In July 2005, the ISGPF developed and published a universal definition and classification scheme for pancreatic fistula, based on the clinical impact of pancreatic fistulas.[5] A broad definition of fistula was developed to include all peripancreatic fluid collections, abscesses, leaks, and fistulas thought to manifest from poor healing of the pancreatic–enteric anastomosis or the transected pancreatic surface: output via an operatively-placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after postoperative day three, with an amylase content greater than three times the upper normal serum value.

Next, in order to differentiate fistula of varying clinical severity, a grading system was proposed based on nine clinical criteria (patient condition, use of specific treatments, ultrasound and/or computed tomography findings, persistent drainage longer than 3 weeks, reoperation, death, signs of infection, sepsis, readmission; Table 2). Grade A fistulae are transient and asymptomatic, evident only by elevated drain amylase levels. Grade B fistulae are symptomatic, clinically apparent fistulas that require diagnostic evaluation and therapeutic management, including antibiotic therapy, supplemental nutrition, somatostatin analogues, and percutaneous drainage. Finally, Grade C fistulas are most severe, and require major deviations in clinical management. In addition to therapeutic interventions, these fistulae result in sepsis, organ dysfunction, even death, and may require surgical exploration for definitive

Table 1 Incidence of pancreatic fistula in 242 patients using four different definitions

Definition		Pancreatic fistula	
		N	%
D1	Output more than 10 cm^3/day of amylase-rich fluid since the 5th postoperative day or for more than 5 days	69	28.5
D2	Output more than 10 cm^3/day of amylase-rich fluid since the 8th postoperative day or for more than 8 days	44	18.5
D3	Output between 25 and 100 cm^3/day of amylase-rich fluid since the 8th postoperative day or for more than 8 days	40	16.5
D4	Output more than 50 cm^3/day of amylase-rich fluid since the 11th postoperative day or for more than 11 days	24	9.9

Adapted from Dig Surg 2004; 21:54–69. [6]

Table 2 Criteria for grading pancreatic fistula (ISGPF classification scheme)

Criteria	No Fistula	Grade A Fistula	Grade B Fistula	Grade C Fistula
Drain amylase	<3 times normal serum amylase	>3 times normal serum amylase	>3 times normal serum amylase	>3 times normal serum amylase
Clinical conditions	Well	Well	Often Well	Ill appearing/bad
Specific treatment	No	No	Yes/No	Yes
US/CT (if obtained)	Negative	Negative	Negative/Positive	Positive
Persistent drainage (> 3 weeks)	No	No	Usually Yes	Yes
Signs of infection	No	No	Yes	Yes
Readmission	No	No	Yes/No	Yes/No
Sepsis	No	No	No	Yes
Reoperation	No	No	No	Yes
Death related to fistula	No	No	No	Yes

Signs of infection include elevated body temperature >38°C, leukocytosis, and localized erythema, induration, or purulent drainage. Readmission is any hospital admission within 30 days following hospital discharge from the initial operation. Sepsis is the presence of localized infection and positive culture with evidence of bacteremia (i.e., chills, rigors, elevated WBC) requiring IV antibiotic treatment, or hemodynamic compromise as demonstrated by high cardiac output and low SVR within 24 h of body temperature >38°C.
Adapted from Surgery 2005; 138:8–13. [5]

management. In sum, Grade A fistulae are *biochemical* while, Grades B and C are considered *clinically relevant*.

Our group recently performed an analysis of this grading system, in an effort to describe the clinical and economic significance of escalating fistula severity.[8] Pancreatic fistula following pancreaticoduodenectomy for benign and malignant disease occurred in roughly 30% of patients; yet, one-half were clinically silent Grade A fistulae. All clinical and economic outcomes for patients with this fistula grade were equivalent to those for patients who did not develop pancreatic fistula. These findings indicate that biochemical evidence of fistula alone has no measurable impact on postoperative outcomes. Grade B and C fistulae, however, resulted in considerably longer hospital stays, higher rates of morbidity, and significantly greater hospital costs (Fig. 1). Furthermore, patients with these clinically relevant fistulae more often required ICU management, hospital readmission, outpatient healthcare resources, and rehabilitative services. While many definitions and classifications of pancreatic fistula are inconsistent and restrictive, the ISGPF grading system may, to date, provide the best and most inclusive scheme for characterizing clinically relevant fistulae.

Risk Factors

Successful prevention and management of pancreatic fistula is also predicated on distinguishing patients at high risk for this ominous complication. Contemporary surgical literature provides specific examples of predictive factors for fistula development, particularly after pancreatoduodenectomy. These elements are appropriately categorized as disease-related, patient-related, and operative risk factors.

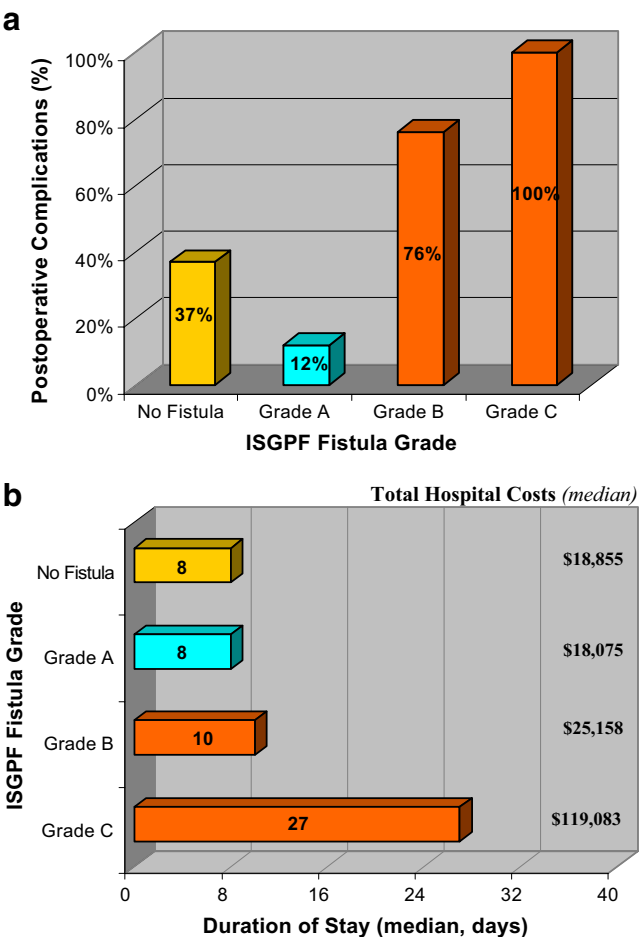

Figure 1 **a** Rates of other postoperative complications given each ISGPF fistula grade. **b** Clinical and economic impact of each ISGPF fistula grade.

Disease-Related Risk Factors

The most widely recognized risk factors for pancreatic fistula are directly linked to disease of the pancreas and/or periampullary region. Principal among these is a soft pancreatic parenchyma. Lin et al. describe the relationship between gland texture and pancreatic fistula development in a series of nearly 2,000 pancreatoduodenectomies.[9] In their study, a soft pancreas was associated with a 22.6% fistula rate, and conferred a 10-fold increased risk of pancreatic fistula versus an intermediate or hard gland. Other investigations have similarly reproduced high rates of pancreatic fistula in the presence of soft pancreatic parenchyma.[1–3,10–12]

A number of studies also implicate the size of the pancreatic duct as a major predictor of fistula.[1,13] Small, non-dilated pancreatic ducts, typically defined as less than or equal to 3 mm in diameter, predispose patients to pancreatic fistula. In one study, 22% of patients with small ducts developed pancreatic fistulae, compared to 7% of patients with dilated ducts. Other disease-related risk factors include pathologic diagnosis (i.e., ampullary or duodenal carcinoma, distal cholangiocarcinoma, intraductal papillary mucinous neoplasia, pancreatic cystadenomas, benign islet tumors, duodenal adenomas) and increased pancreatic juice output.[4,9]

Patient-Related Risk Factors

Patient characteristics have also been considered as predictive factors for pancreatic fistula, including age, gender, coronary artery disease, jaundice, creatinine clearance, and neoadjuvant therapy. Matsusue et al. prospectively examined 100 consecutive patients who underwent pancreatoduodenectomy with pancreaticojejunostomy.[14] In this cohort, patient age greater than 70 years was the only factor associated with poor anastomotic healing and pancreatic fistula. A number of studies have also suggested that male gender predisposes patients to pancreatic fistula.[9,13] Lin et al. provide convincing evidence that a history of coronary artery disease correlates with pancreatic fistula.[9] Findings from the multivariate analysis indicate that patients with coronary artery disease have nearly a four-fold increased likelihood of developing a pancreatic fistula. The authors intimate that coronary artery disease may compromise anastomotic healing by decreasing visceral perfusion. Other previously identified patient-related risk factors include the duration of jaundice and creatinine clearance.[11] Yeh et al. suggest that the *duration* of jaundice, rather than the *extent* of jaundice, determines the development of pancreatic fistula. Their findings demonstrate that the average duration of jaundice among patients with pancreatic fistula was nearly twice as long as that among patients in the no fistula group: 45±21 days versus 23±11 days (p=0.018). Serum bilirubin level had no meaningful impact on fistula development. In the same study, pancreatic fistula was associated with a significantly lower creatinine clearance: 59±18 ml/min versus 71±14 ml/min (p=0.005). The authors propose that impaired creatinine clearance, defined as <50 ml/min, precipitates acute renal failure, intra-abdominal bleeding, and sepsis; processes that predispose patients to pancreatic fistula, particularly those with obstructive jaundice. Alternatively, diabetes mellitus and neoadjuvant chemoradiation therapy have been shown to offer a protective benefit against pancreatic fistula, with the latter presumably causing a decrease in pancreatic exocrine secretion.[15,16]

Operative Risk Factors

Technical considerations have been rigorously scrutinized during the past two decades in an effort to identify operative factors associated with increased fistula rates. Various techniques for managing the pancreatic remnant have been compared, including pancreaticojejunostomy versus pancreaticogastrostomy; the duct-to-mucosa versus invagination pancreaticojejunal anastomosis; stent versus no stent across the pancreatic–enteric anastomosis; single versus double Roux-en-Y loop reconstruction; and the use of somatostatin analogues and/or fibrin sealants. These techniques will be discussed further.

Apart from these technical considerations, increased intraoperative blood loss is an important operative risk-factor-associated pancreatic fistula. In the study conducted by Yeh et al., the pancreatic fistula group suffered significantly greater blood loss than their no fistula counterparts: 1584±862 ml versus 794±387 ml (p=.0005).[11] The investigators proposed that patients with intraoperative blood loss exceeding 1,500 ml are at higher risk of fistula development. Their results also indicate that this scenario is associated with more advanced stages of disease (i.e., portal or superior mesenteric vein invasion), adhesions due to prior operations, patient obesity, jaundice-associated coagulopathy, and concurrent pancreatitis.

Summary

Risk factors for pancreatic fistula following pancreatoduodenectomy include pancreatic texture, pathology, duct size, pancreatic juice output, age, gender, coronary artery disease, duration of jaundice, creatinine clearance, diabetes mellitus, neoadjuvant therapy, operative technique, stents, pharmacologic adjuvants, adhesive sealants, and intraoperative blood loss. We recently examined outcomes for 233 consecutive pancreatoduodenectomies at our institution and analyzed these risk factors under the framework of the ISGPF grading system.[17] We found that (1) small pancre-

atic ducts less than or equal to 3 mm in diameter; (2) soft pancreatic parenchyma; (3) ampullary, duodenal, cystic, or islet cell pathology; and (4) intraoperative blood loss greater than 1,000 ml were associated with an increased risk of developing a clinically relevant pancreatic fistulae (Grades B and C); there were no verifiable risk factors for biochemical Grade A fistulae. We also revealed that an additive risk effect exists, as an increase in these four risk factors significantly impairs surgical recovery, prolongs hospital stays, and equates to substantial increases in hospital costs (Table 3).

Risk factors for pancreatic fistula following distal pancreatectomy are poorly understood. There has been some suggestion that overweight patients (i.e., body mass index greater than 25 kg/m^2) have an increased risk of pancreatic fistula, but no plausible explanation has been described.[18] Pannegeon et al. identified transections at the pancreatic body and the absence of pancreatic duct ligation as two verifiable risk factors for pancreatic fistula during distal pancreatectomy.[19] Ridolfini et al. also provide a meaningful analysis of risk factors for pancreatic fistula from a series of 64 consecutive distal pancreatectomies, utilizing the ISGPF grading system.[20] Over a 10-year period, 14 of 64 patients (22%) developed pancreatic fistulae; of these, four (29%) were classified as Grade A, nine (64%) were Grade B, and one (7%) was Grade C. The authors suggest that malignant or benign disease of the pancreas, soft pancreatic tissue, spleen-preserving procedures, and the lack of postoperative prophylactic octreotide were associated with significantly higher rates of pancreatic fistula. Age, gender, and technique of pancreatic stump closure, in this analysis, were not associated with fistula development. Further analyses are necessary to determine the clinical impact of these and other risk factors.

Clinical Course

The impact and severity of pancreatic fistula have been described in a number of recent studies.[1–3,7–10,21–24] Among these series, the incidence of pancreatic fistula ranged between 6% and 14%, and this complication remained the most influential factor associated with operative death, increased morbidity, longer hospital stays, and greater hospital costs. In 1997, van Berge Henegowen et al. published results from a retrospective study of 269 patients.[1] Overall, only ten deaths (3.7%) occurred, either in-hospital or within 30 days. The leading cause of death was pancreatic fistula (eight of the ten patients). Between 1990 and 1996, Yeo et al. observed a similar phenomenon at their institution, where only nine operative deaths (1.4%) occurred among 650 patients; six were attributed to pancreatic fistulae.[22] Beyond operative mortality, pancreatic fistula is associated with other non-fistulous complications, particularly delayed gastric emptying, ileus, wound infection, intra-abdominal abscess, pancreatitis, hemorrhage, and sepsis. Rates of reoperation and hospital readmission are also significantly increased, as well as hospital costs.[2–3,8–9,25]

Little is known about the impact of pancreatic fistula in other types of pancreatic resection. Its incidence after distal pancreatectomy is presumed to be less than that following pancreaticoduodenectomy.[26–28] The single largest series of distal pancreatectomy, reported by Lillemoe et al., examined outcomes for 235 patients, of which only 12 (5%) developed pancreatic fistulae.[29] Higher rates of pancreatic fistula should be anticipated in central pancreatectomy, which range from 20% to 63% among specialized centers.[30–34] It is presumed that these higher rates are due to the creation of two pancreatic remnants in this procedure and, thus, two potential sites for fistula formation. However, valid conclusions in this resection modality will require additional investigations and larger operative series.

At our institution, we analyzed and compared the clinical and economic effects of pancreatic fistulae among patients undergoing pancreatoduodenectomy, distal and central pancreatectomy.[24] The incidence of clinically relevant fistulae (Grades B and C, according to the ISGPF grading system) was 16% for pancreatoduodenectomy, 13% for distal pancreatectomy, and 83% for central pancreatectomy. The clinical course of these fistulas depended on the type of

Table 3 The impact of increasing number of risk factors for pancreatic fistulae

Outcomes	No risk factors n=63	1 risk factor n=88	2 risk factors n=66	3 risk factors n=13	4 risk factors n=3	p value
Clinically relevant fistulae (%)	1 (2)	7 (8)	16 (24)	4 (31)	3 (100)	<.001
Non-fistulous complications (%)	22 (35)	38 (43)	38 (58)	6 (42)	2 (67)	0.113
Hospital duration (median, days)	8	8	8	9	19	0.001
Total hospital costs (median)	$16,969	$17,797	$20,179	26,776	$40,517	0.002
Total cost-increase (beyond no risk factors)	–	$828	$3,210	$9,807	$23,548	–

Risk factors for pancreatic fistulae consist of (1) small pancreatic duct size (<3 mm); (2) pancreatic parenchyma of soft texture; (3) ampullary, duodenal, cystic, or islet cell pathology; and (4) increased intraoperative blood loss (>1,000 ml).
Adapted from World J Surg 2007; 32:419–428.[17]

resection performed. A clinically relevant fistula after pancreatoduodenectomy and central pancreatectomy was an acute manifestation, and often required aggressive management in intensive care settings. Surgical exploration, when indicated, was urgent and usually occurred early in the postoperative period. Patients usually benefited from rehabilitation placement for continued postoperative care, as these clinical fistulae were often associated with other complications, such as wound and respiratory infections. Patients with clinically relevant fistulae after distal pancreatectomy seldom required aggressive management approaches or experienced extended hospital stays. Patients were typically discharged home rather than to rehabilitation facilities. Prolonged drainage of intra-abdominal collections of more than three weeks and multiple hospital readmissions, usually for image-guided percutaneous drainage, were almost always required.

Preventive Approaches

Technical Modifications

Management of the pancreatic remnant has been extensively studied with the aim of preventing and mitigating the impact of pancreatic fistula. Technical considerations in pancreatoduodenectomy include, but are not limited to, the type of anastomosis (pancreaticojejunostomy vs. pancreaticogastrostomy), the creation of a duct-to-mucosa or invagination anastomosis, the placement of a stent across the pancreatic–enteric anastomosis, and the type of Roux-en-Y loop reconstruction. For distal pancreatectomy, pancreatic duct ligation, staple versus suture closure of the pancreatic stump, and sealing by use of fibrin glue. Pancreatoduodenectomy—first performed by Kausch in 1912, and later reported by Whipple et al. in 1935—traditionally utilizes a pancreaticojejunostomy to reconstruct the pancreatic remnant.[35–36] This method re-establishes enteric flow of pancreatic juice after the pancreatic head and duodenum are resected by uniting the remaining pancreatic tissue with a loop of jejunum. The jejunum is a logical choice for a pancreatico-enteric anastomosis due to its generous blood supply and mobile mesentery; yet, during the past 30 years, this technique has consistently been reported to yield, on average, a 10% fistula rate (range: 2–19%).[37]

Pancreaticogastrostomy has gained favor in recent years as a reasonable alternative to pancreaticojejunostomy. It was introduced by Waugh and Claggett [38] in 1946, but has seldom been employed in large operative series. This reconstruction is typically accomplished by anastomosing the pancreatic remnant to the posterior gastric wall.[39] Compared to the classical pancreaticojejunostomy, its putative advantages are three-fold. First, the thick gastric wall and its rich blood supply are suitable for anastomotic healing. Second, the proximity of the stomach to the pancreas allow for a tension-free anastomosis. Finally, the presence of gastric acid incompletely activates pancreatic enzymes, and therefore, prevents disruption of the sutured anastomosis.[40] A number of studies compare this technique with the pancreaticojejunostomy reconstruction, most notably that of Yeo et al., which randomized 145 consecutive patients to undergo pancreatoduodenectomy with either a pancreaticogastrostomy or pancreaticojejunostomy.[39] The groups were comparable with respect to rates of pancreatic fistula (12.3% for pancreaticogastrostomy, 11.1% for pancreaticojejunostomy), and the authors conclude that pancreaticogastrostomy confers no additional benefit and is not associated with a lower incidence of pancreatic fistula. Several other studies have supported these conclusions, as this technique has yet to gain widespread acceptance.[4,40] We consequently reestablish pancreatic–enteric continuity with a pancreaticojejunostomy.[8,24]

Variations to the pancreaticojejunostomy include the duct-to-mucosa anastomosis, end-to-end (dunking) invagination, and end-to-side invagination. The duct-to-mucosa anastomosis sews the pancreatic duct directly to the bowel mucosa in either a continuous or interrupted fashion, similar to many other gastrointestinal and vascular anastomoses; invagination incorporates both the pancreatic duct and serosal layer into the bowel. Data from recent literature suggests that the duct-to-mucosa anastomosis is associated with lower fistula rate.[3–4,41–43] It is our practice to perform an interrupted duct-to-mucosa anastomosis and reinforce the serosal layer with several silk sutures.[8,24]

Some surgeons recommend placement of stents across the pancreaticojejunostomy for internal or external drainage of exocrine pancreatic secretion. It has been argued that this approach protects the pancreatic duct from iatrogenic injury and facilitates more precise placement of sutures during the duct-to-mucosa anastomosis. There are clinical reports of decreased rates of pancreatic fistula with this technique, [44,45] but an equal number of studies observed either no benefit or potential harm with routine use of transanastomotic stents.[3,14] To date, there remains no conclusive data to support or oppose this technical approach. We prefer to use an internal 5-Fr pediatric feeding tube when the pancreatic duct is less than or equal to 3 mm in diameter.[17]

Additionally, some surgeons advocate for the use of separate jejunal limbs to isolate the pancreatic anastomosis from the biliary anastomosis.[41,46] The addition of a Roux loop to the standard drainage configuration may limit activation of pancreatic enzymes by biliary secretions, a process that often occurs when a singular pancreatobiliary limb is employed. However, this benefit is yet to be proven in a prospective or randomized study. In our practice, we favor a single pancreatobiliary drainage limb when creating

the pancreatic and biliary anastomoses; the latter is constructed 10 cm distal to the pancreaticojejunostomy.[8,24]

Management of the pancreatic remnant during distal pancreatectomy includes pancreatic duct ligation, staple versus suture closure of the pancreatic stump, and fibrin sealing of the pancreatic remnant.[19,20,27–29,47,48] Bilimoria et al. reviewed their experience with these techniques in a series of 126 distal pancreatectomies performed between 1990 and 1996.[47] Successful ligation of the main pancreatic duct occurred in 73 patients (58%), and was the only closure technique associated with a significant decrease in pancreatic fistula rates: 9.6% for duct ligation versus 34.0% for no ligation (p=.001). The authors conclude that there is a clear benefit with direct ligation of the pancreatic duct. A recent meta-analysis conducted by Knaebel et al. examined other techniques for distal pancreatectomy closure.[27] Their findings demonstrate no significant difference between handsewn and stapler closure of the pancreatic remnant. Fibrin glue applied to the cut end of the pancreatic remnant appears to reduce rates of fistula, but current investigations of this technique have been criticized for high selection bias. At our institution, we typically divide the pancreatic parenchyma with a linear stapler device and oversew the staple line with fine polypropylene sutures. A tongue of omentum is often secured to the pancreatic stump with silk sutures to reinforce the closure; fibrin glue is seldom applied.[24]

Prophylactic Octreotide

Octreotide is a potent and long-acting synthetic analogue of somatostatin, which inhibits the secretion of cholecystokinin, secretin, glucose dependent insulinotropic peptide, vasoactive intestinal polypeptide, insulin, and glucagons. Its relevance in pancreatic surgery lies in its inactivation of gastric and pancreatic exocrine secretion, its potential to harden the pancreatic parenchyma, and its ability to facilitate construction of a delicate pancreatic–enteric anastomosis. Prophylactic octreotide, administered preoperatively and/or intraoperatively, may modify the risk for pancreatic fistula and reduce the incidence of other gastrointestinal complications.[49]

The effects of somatostatin analogues have been explored in several randomized trials, which are either in favor of, [50,51] or in opposition to, [7,10] prophylactic octreotide. These differences are attributed to small sample sizes, concurrent analyses of several resection types, high selection bias, and the lack of a unifying consensus definition of pancreatic fistula. We recently sought to circumvent these problems by examining the impact of prophylactic octreotide in a large series of patients with identifiable risk factors for pancreatic fistula under the framework of the International Study Group on Pancreatic Fistula (ISGPF) grading system.[52] In our retrospective analysis, high-risk glands referred to patients with *at least one risk factor* for pancreatic fistula: (1) small pancreatic ducts less than or equal to 3 mm in diameter; (2) soft pancreatic parenchyma; (3) ampullary, duodenal, cystic, or islet cell pathology; and (4) intraoperative blood loss greater than 1,000 ml. Low-risk glands connoted patients *with no risk factors*. Prophylactic octreotide offered no benefit when administered—without consideration of risk severity—to all patients. Rates of pancreatic fistula and other non-fistulous complications, as well as average hospital duration and costs, were equivalent between the *Octreotide* and *No Octreotide* groups.

The efficacy of prophylactic octreotide, however, was improved by selective administration in the setting of a high-risk gland. While prophylaxis had no effect in the overall clinical series, it was beneficial when administered exclusively to patients with high-risk glands. Those who received prophylactic octreotide were less likely to develop clinically relevant fistulae (Grades B and C) than those in the *No Octreotide* group. Prophylactic octreotide did not influence clinically relevant fistula rates among patients with low-risk glands.

There are three explanations for these outcomes. First, the presence of risk confers a two-fold increase in the incidence of all degrees of pancreatic fistulae (Grades A to C). Second, when pancreatic fistula occurs in patients with low-risk glands, they are typically of biochemical Grade A severity; fistulae in the setting of high-risk glands most often have a measurable clinical impact (Grade B/C). Finally, when administered exclusively among patients with high-risk glands, prophylactic octreotide reduces the ratio of clinically relevant fistulae to biochemical fistulae (Fig. 2). In our practice, we selectively administer octreotide (intraoperatively) to patients with either soft glands or

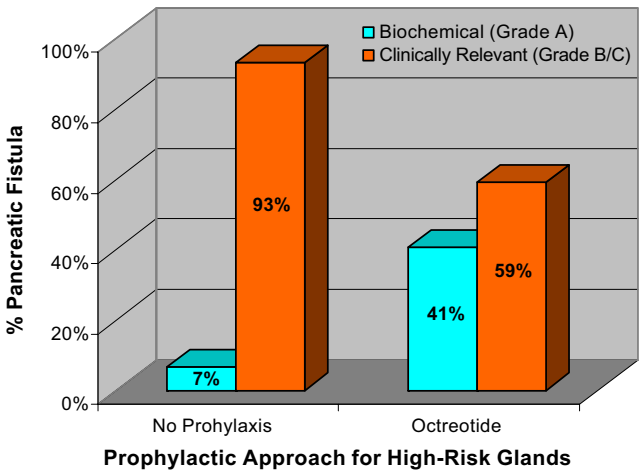

Figure 2 Prophylactic octreotide reduces the severity of pancreatic fistulae in high-risk glands.

small pancreatic ducts; in those harboring ampullary, duodenal, cystic, or islet conditions; or in cases where intraoperative blood loss is excessive. To date, the only randomized trial examining octreotide in distal pancreatectomy (Suc et al. [53]) does not support prophylactic administration, and it is our practice not to employ this pharmacologic adjuvant in such resections.

Management Approaches

Diagnosis of Pancreatic Fistula

Successful postoperative management of pancreatic fistula relies on its early identification and diagnosis. Patients may report abdominal pain, nausea, vomiting, and/or failure to pass flatus or stool. Clinical signs are nonspecific, and usually include fever greater than 38 °C or 101 °F; postural hypotension; a tender, distended, or rigid abdomen; and localized abdominal or wound erythema, warmth, or swelling.

Evaluation of effluent from an intra-abdominal drain is the primary diagnostic tool, as high amylase contents, generous fluid outputs, and sinister fluid appearances warrant further evaluation. Amylase concentrations greater than three times the upper limit of normal serum value often confirm the presence of an amylase-rich fluid collection. This threshold will likely vary across institutions—300 IU/L at our institution [8]—and we often use a level greater than 1,000 IU/L as an indication for cautious management. Surgeons are often in disagreement as to which day amylase levels should be measured. In accordance with an institutional clinical pathway for pancreatic resection, we typically measure drain amylase content after tolerance of a soft solid diet, usually on or after postoperative day six; deviations from this pathway often signify the onset of complications, particularly that of pancreatic fistula, abscess, or hemorrhage.[54]

It has been suggested, most notably by Traverso and colleagues, that the daily volume of drainage provides for early detection of pancreatic fistula.[55] Their work represents an in-depth analysis of drain volumes and amylase content in 207 consecutive patients who underwent pancreatoduodenectomy from 1996 to 2002. Pancreatic fistula was defined as drainage greater than 30 ml per day (after postoperative day five) *plus* an amylase-rich fluid greater than five times the normal serum value. Patients were classified as having no fistula, biochemical (asymptomatic) fistula, or clinical (requiring therapeutic intervention, reoperations, readmission, or prolonged hospital duration) fistula. Drainage of more than 30 ml per day *and* high amylase content had a positive predictive value of 59% for clinically relevant fistula. This predictive value increased to 84% when a combination of more than 200 ml per day of drainage *and* high amylase content was employed (Table 4). This study provides convincing data that daily drainage volumes greater than 200 ml on or after postoperative day five likely indicate the presence of clinically relevant pancreatic fistulae.

Finally, any suspicious or sinister appearance to the effluent (i.e., change in color or purulence) should be examined further. We obtain white blood cell counts, Gram stains and cultures in these scenarios. As the process evolves, the clinical signs and symptoms of fistula may become more apparent; and it is reasonable to obtain further imaging studies. It is our practice to perform abdominal computed tomography when fever, leukocytosis (i.e., white cell count greater than 10,000/mm^3), or sinister effluents are present, although it is often difficult to distinguish normal postoperative fluid accumulations from pancreatic fistula. Computed tomography may or may not confirm the presence of peripancreatic fluid collections, but in patients with risk factors for fistula, the index of suspicion is high.[24] Other imaging modalities include abdominal ultrasound, drain studies, magnetic resonance imaging, and pancreatography.[56,57]

Management of Pancreatic Fistula

Non-operative management of pancreatic fistula includes traditional, albeit empirical, treatments for postoperative ileus and intra-abdominal collections.[24,56–58] Patients are made nil per os (NPO) and provided adequate fluid hydration. Parenteral nutritional support may be administered to patients who have not yet tolerated oral intake, and/or those presenting on or after postoperative day 10. Empiric antibiotics are given if signs of infection (i.e., fever, leukocytosis, purulent drainage, erythema, warmth, tenderness) are present, and adjusted depending on information from Gram stains or cultures. Intra-abdominal drains are left in situ until daily drainage volumes approach 50 ml per day; patients can be discharged home as long as the character of the drainage is not purulent or particulate. Cautious drain management (i.e., in situ drainage) is indicated for patients with high-output drainage (greater than 200 ml per day) *and* amylase-rich effluent (greater

Table 4 Predictive values for a clinically relevant fistula utilizing drain information obtained on postoperative day 5

On POD 5	PPV	NPV
>5× amylase only	45%	100%
>30 ml/day only	11%	100%
>200 ml/day only	21%	99%
>5× amylase+30 ml/day	59%	100%
>5× amylase+200 ml/day	84%	99%

POD Postoperative day, *PPV* positive predictive value, *NPV* negative predictive value
Adapted from J Gastrointest Surg 2006; 10:490–498.[55]

than 1,000 IU/L). Therapeutic octreotide can also be administered to reduce pancreatic secretions, typically until oral intake resumes and/or hospital discharge occurs.

CT- or ultrasound-guided percutaneous drainage is considered at the discretion of the surgeon. We usually employ this modality for large fluid collections that have not responded to conservative therapies, but which are amenable to drainage. This is more often required after distal pancreatectomy, whose fistulas typically follow a protracted clinical course.[24] Surgical exploration is seldom required, but is indicated when anastomotic dehiscence is suspected and for patients who deteriorate clinically, often in the setting of a non-drainable abscess, sepsis, or multiple organ dysfunction.[8,24,56–58] Four options are to be considered, including wide peripancreatic drainage of an abscess or fluid collection, revision of the initial pancreatico-enteric anastomosis, conversion to an alternative pancreatico-enteric anastomosis, or completion (i.e., total) pancreatectomy.

Conclusion

Pancreatic resection is now considered a safe and effective operative endeavor for management of pancreatic adenocarcinoma, periampullary neoplasms, pancreatitis, cystic and neuroendocrine lesions. It is now associated with low mortality rates, shorter hospital stays, and modest improvements in postoperative morbidity. Pancreatic fistula—leakage from the pancreatico-enteric anastomosis or the transected pancreatic surface—is a significant problem after pancreatoduodenectomy, distal and central pancreatectomy. This review provides a thorough evaluation of definitions, risk factors, preventive approaches, and management strategies for this difficult complication.

The definition and grading system put forth by International Study Group on Pancreatic Fistula is now the standard consensus definition for pancreatic fistula. Utilization of the classification scheme in randomized trials and prospective studies should enable accurate and objective comparisons of operative techniques and surgical experiences going forward. There are numerous risk factors for the clinically relevant fistula types, but soft pancreatic parenchyma; small pancreatic ducts; ampullary, duodenal, cystic, and islet cell pathology; and excessive intraoperative blood loss are most influential. Preventive approaches—including technical and anastomotic modifications, and prophylactic octreotide—should be implemented in patients deemed to be high-risk for pancreatic fistula. Successful management of this troublesome complication depends on early detection and a high index of suspicion. Analysis of drain data is the principal diagnostic tool, but computed tomography, ultrasound, and pancreatography provide additional information. Non-operative management strategies include maintaining fluid balance, providing parenteral nutritional support, and administering antibiotics or octreotide. Image-guided drainage or surgical exploration is indicated if large fluid collections persist and/or patients deteriorate clinically.

Although experience with pancreatic fistula is long-standing, pancreatic surgeons continue to invest significant effort to improve perioperative management of this complication. As current fistula rates hover around 15%, the future success of our field will most likely require better diagnostic approaches, novel management algorithms randomized clinical trials, multi-institutional investigations, and multi-disciplinary collaboration in order to reach the “zero percent” mark.

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A Case of Peribiliary Cyst Presenting with Obstructive Jaundice

Naoki Ikenaga · Kazuo Chijiiwa · Kazuhiro Otani · Jiro Ohuchida · Shuichiro Uchiyama

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Abstract A 77-year-old woman with a complaint of itching was shown to have an elevated serum bilirubin level. She had no history of liver disease. Computed tomography and magnetic resonance cholangiopancreatography revealed a 17-mm-diameter cystic lesion obstructing the main hepatic duct at the hepatic hilum. Drip infusion cholangiographic computed tomography and endoscopic retrograde cholangiography showed that the cyst did not communicate with the biliary tree; thus, a peribiliary cyst was diagnosed. Cystectomy was performed, and the jaundice resolved. Peribiliary cysts are generally asymptomatic and rarely cause obstructive jaundice. They are usually multiple and caused by an underlying liver disorder with a poor prognosis. Our case suggests that peribiliary cysts can arise in healthy liver and cause symptoms. Cystectomy is the treatment of choice if the cyst is solitary.

Keywords Peribiliary cyst · Obstructive jaundice · Stenosis · Resection · Cystectomy

Case History

A 77-year-old woman with mild jaundice and itching was admitted to our hospital. Laboratory tests showed elevated levels of serum total bilirubin (2.6 mg/dL), aspartate aminotransferase (205 IU/L), alanine aminotransferase (348 IU/L), gamma-glutamic transpeptidase (101 IU/L), lactic dehydrogenase (307 IU/L), and alkaline phosphatase (696 IU/L). The patient had no history of liver disease or alcohol abuse. Serologic markers for viral hepatitis were negative. Imaging studies, including ultrasonography, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) revealed a unilocular cyst, 17 mm in diameter, at the hepatic hilum (Fig. 1a). Drip infusion cholangiographic (DIC) CT showed stenosis of the main hepatic duct adjacent to the cyst and dilatation of the left distal hepatic duct. The cyst did not communicate with the lumen of the biliary tree (Fig. 1b). Endoscopic retrograde cholangiography (ERC) showed a filling defect of the main hepatic duct with a smooth lumen (Fig. 2a). Intraductal ultrasonography (IDUS) revealed that the cyst compressed the main hepatic duct at the stenotic site (Fig. 2b). A peribiliary cyst with obstructive jaundice was diagnosed, and cystectomy was performed. The cyst, which was located at the hepatic hilum, compressed and adhered tightly to the hepatic duct (Fig. 3). T-tube drainage was added after cystectomy because the hepatic duct was incidentally opened. The resected specimen consisted of a cystic lesion containing serous fluid. The cyst wall was thin, and there was no mural nodule. Histological examination revealed that the cyst wall was composed of thin fibrous tissue, lined by a single layer of cuboidal epithelium without cellular atypia (Fig. 3, inset). An aggregation of small bile ducts was noted in the wall. Postoperatively, laboratory values normalized and DIC-CT revealed the absence of the hepatic duct stenosis after removal of the choledochal T-tube.

N. Ikenaga · K. Chijiiwa (✉) · K. Otani · J. Ohuchida · S. Uchiyama
Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine,
5200 Kihara, Kiyotake,
Miyazaki 889-1692, Japan
e-mail: kazuochi@med.miyazaki-u.ac.jp

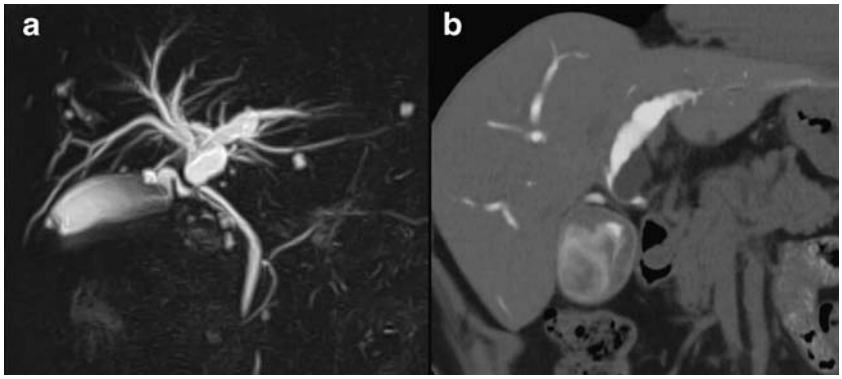

Figure 1 **a** MRCP revealed a unilocular cyst, 17 mm in diameter, at the hepatic hilum. **b** DIC-CT revealed a cyst compressing the hepatic duct and dilatation of the left distal hepatic duct. The cyst did not communicate with the biliary tree.

Discussion

Peribiliary cysts, which were first described in 1984 by Nakanuma et al.,[1] originate from cystic dilatation of the extramural peribiliary glands of the bile duct. Inflammation and circulatory disturbance in the liver are considered possible mechanisms of cystic formation because the cysts are found mainly in patients with severe liver disease, such as alcoholic liver dysfunction, portal hypertension, or thrombosis.[1–4] Genetic factors may also be involved in the pathogenesis of peribiliary cysts, which have been found in patients with autosomal dominant polycystic kidney disease.[2,5] Terada et al.[2] reported that cystic change in peribiliary glands was found in 20.2% of autopsied livers, but this disease is rarely encountered in clinical practice, probably because the cysts are usually less than 10 mm in diameter and the disease itself is poorly recognized. Only about 60 cases of hepatic peribiliary cyst have been reported.[6,7] Image findings are important for the diagnosis of peribiliary cyst. These cysts are usually located along portal tracts and are difficult to distinguish from a dilated bile duct upon CT and MRCP because density and signal intensity of the cysts are similar to those of the biliary tree. DIC-CT and ERC are considered very useful in making this distinction because peribiliary cysts do not communicate with the lumen of the biliary tree. In our case, DIC-CT clearly depicted a cystic lesion not filled with contrast medium and compressing the hepatic duct, causing severe stenosis and dilatation of the distal bile duct. Moreover, IDUS clearly visualized the internal structure of the cyst as anechoic, and the round smooth lumen with no mural nodule was not indicative of a malignant tumor. On the basis of these findings, we concluded that the solitary peribiliary cyst caused the patient's obstructive jaundice and liver dysfunction. Peribiliary cysts are usually multiple, occur on a background of liver disease, and are considered clinically harmless. There have been only six reported cases in which obstructive jaundice developed, and in all six, there were multiple lesions on a background of severe liver disease with a poor prognosis.[7–9] In our case, the peribiliary cyst was unlike those previously reported because it was macroscopically solitary and the patient's liver was healthy. Moreover, the obstructive jaundice was successfully relieved by cystectomy, and the clinical course

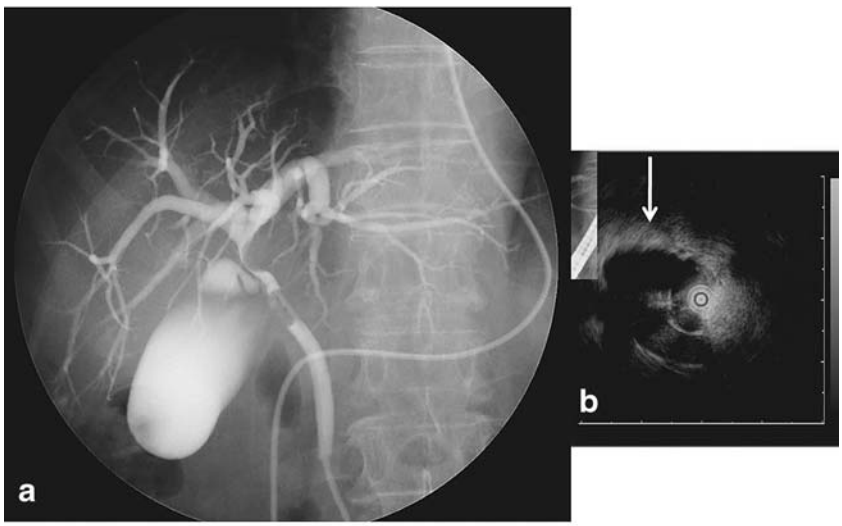

Figure 2 **a** Balloon ERC showed a filling defect at the main hepatic duct. **b** IDUS showed a cyst (*arrow*) compressing the hepatic duct at the stenotic site.

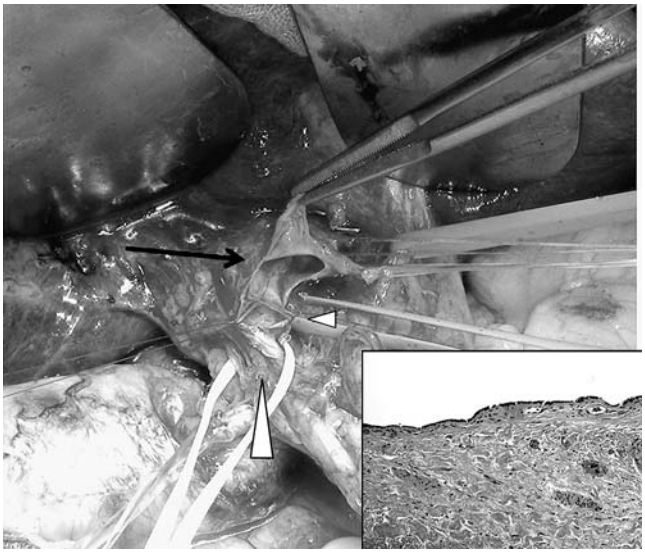

Figure 3 The cyst (*arrow*), which was located at the hepatic hilum, compressed and adhered tightly to the main hepatic duct. The common hepatic duct was encircled (*large arrowhead*) and opened incidentally (*small arrowhead*). The cyst wall was composed of cuboidal epithelium (*inset*).

after surgery was uneventful. To the best of our knowledge, no similar case has been reported.

Peribiliary cysts can occur in normal liver and cause symptoms, such as jaundice and itching. Cystectomy seems to be an effective procedure to relieve the symptoms if the cyst is solitary.

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Giant Trichobezoar and Gastric Perforation in a Normal Healthy Woman

Amanpal Singh · Tina Kochar · Advitya Malhotra

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Abstract We present a case report of a mentally healthy woman who had gastric trichobezoar leading to perforation. A pertinent review of literature is included.

Keywords Gastric perforation · Trichobezoar · Mentally healthy

Case Report

A 28-year-old female presented to the emergency department with excruciating epigastric pain that started after she felt a pop in her stomach. The pain was stabbing in nature and associated with a feeling of nausea. Before this episode, she reported a history of intermittent abdominal pain for a period of 2 months. Her history was unremarkable, but her mother and husband reported later that they had stopped her from pulling and eating her own hair. She was married, had two children, and gave no history of any mental illness. A physical examination revealed a muscular defense in the epigastric region. Abdominal computed tomography (CT) showed free air under the diaphragm, a break in the anterior gastric wall, and a large heterogeneous mass in the stomach (Fig. 1). An initial diagnosis of foreign body/bezoar with perforated ulcer was made. The patient underwent an emergent laparotomy, which revealed a large trichobezoar and a perforation on the anterior wall of the stomach (Fig. 2). The bezoar was extracted through an anterior longitudinal gastrotomy. Both the gastrotomy and the perforation were then sutured with regional omental patch. The postoperative period was uneventful. Later, during the outpatient clinic follow-up, patient was noted to wear a short hair style and a cap. She had done this to avoid picking up on her hair.

A. Singh (✉) · T. Kochar · A. Malhotra
University of Texas Medical Branch,
Galveston, TX, USA
e-mail: amasingh@utmb.edu

Discussion

Trichobezoars are foreign bodies formed in gastrointestinal tract because of hair accumulation. In 1935, Debakey and Oschner described that this condition is more common in women especially teenagers.[1] The disease is most often associated with trichotillomania and trichophagia. These psychological diseases are also common in similar population.[2] Other predisposing factors include gastric surgery especially bariatric surgery.[3] The mechanism behind this is not completely settled. Delayed gastric emptying in patients with vagotomy is one of the hypotheses,[4] although some studies have found no difference in the gastric emptying time for solids in patients with and without surgery.[5] Our patient had no psychiatric history. She was a normal healthy woman with no past surgical or medical history.

Abdominal pain is a common clinical presenting symptom.[6] We found rare reports of bezoars presenting with anemia[7] and obstruction, especially when located in the small bowel.[8] Gastric perforation has been reported with trichobezoars.[9,10] Our case is unique in that the patient had no history of any psychiatric disturbance. Her first presentation was with acute abdomen. Clinical suspicion should be high for trichobezoars in women with psychiatric problems and presenting with abdominal pain.

If suspected, trichobezoars can be diagnosed with radiological and endoscopic techniques. Radiological modalities include barium study, ultrasonography, and CT with

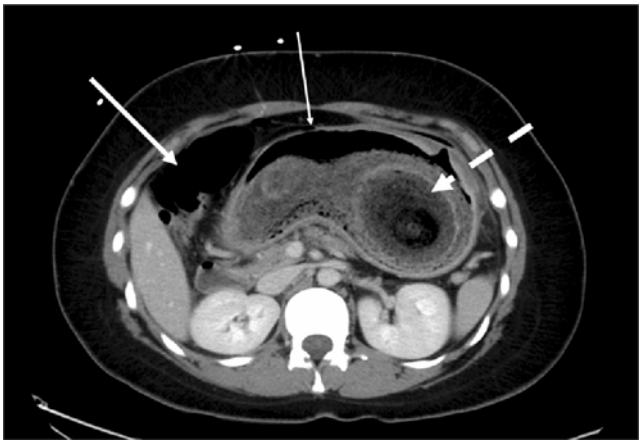

Figure 1 Computed tomographic scan of the abdomen revealing a large heterogeneous mass in the stomach (*broken arrow*), a break in the anterior gastric wall (*thin arrow*), and free air under the diaphragm (*thick arrow*).

the latter proven to have better efficacy.[11] CT findings have been described as heterogeneous mass with air inside. In our case, CT was not only diagnostic of trichobezoar, but also revealed the defect in gastric wall and free air in the abdomen. It also helps to evaluate the rest of the bowel for multiple trichobezoars. Endoscopic techniques have two advantages: one, it allows us to see an extension of trichobezoar in the intestine, and two, it can be used to remove small trichobezoars.[12,13] Laparoscopic removal has been used by some surgeons and may be used more in the future.[14–16] Until there is more widespread experience with these new techniques, the standard means of treatment are laparotomy and gastrostomy.[17] Especially in a complicated case like that of our patient, who presented acutely with gastric perforation and had a large gastric trichobezoar, laparotomy may still be considered the ideal approach.

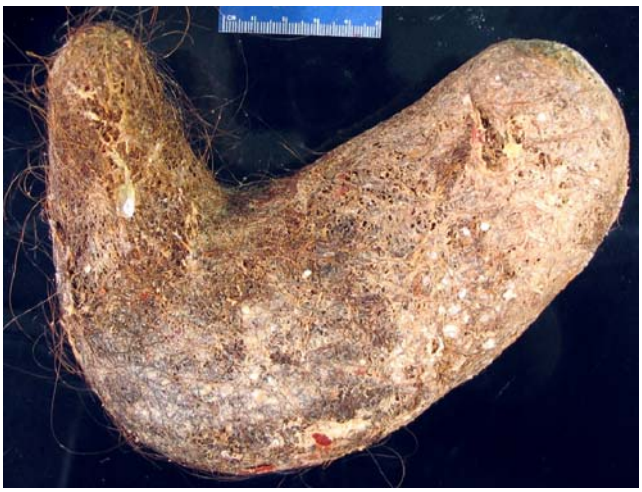

Figure 2 A large trichobezoar.

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Peri-operative Morbidity Affects the Long-Term Survival in Patients Following Liver Resection for Colorectal Metastases

Mettu S. Reddy · Shahid Farid · Rajendra Prasad

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To the Editor,
Journal of Gastrointestinal Surgery
Dear Sir,

We read the article[1] "Peri-operative morbidity affects the long-term survival in patients following liver resection for colorectal metastases" with interest. The authors have used a standardized classification system to grade complications after liver resection for colorectal metastases. They have found that peri-operative morbidity is a predictor of overall and disease-free survival after resection of colorectal liver metastases.

However, we have concerns regarding the methodology used in the analyses. Five patients had grade 5 complication, i.e., peri-operative mortality. According to the authors, overall survival in the peri-op complication group was significantly higher on univariate analysis even when peri-operative mortality was excluded. However, it is not clear whether complications were still a predictive factor for overall survival when peri-operative mortality was excluded in the multivariate analysis. Similarly, there is no mention as to whether peri-operative mortality was excluded before analysis to identify predictors for disease-free survival.

M. S. Reddy (✉) · S. Farid · R. Prasad
Department of Hepatobiliary & Transplantation Surgery,
St James's University Hospital,
Leeds, UK
e-mail: mettu.reddy@sunderland.ac.uk

The authors then subdivided patients with complications into mild (grades 1 and 2) and severe (grades 3, 4, and 5) groups and compared survival between the two subgroups. The authors' claim that the subgroup with serious peri-operative complications (n=27) had significantly poorer survival cannot be supported, as nearly 20% of patients in the serious complication group had already died by the start of follow-up. It is also confusing because they have compared two subgroups of patients within the complication group and then state that patients with nil or minor complications had better survival. A better way to analyze the data would have been to censor the data for early mortality before carrying out long-term survival analysis.

The authors hypothesize that the peri-operative complications induce a period of immunosuppression in these patients which allows residual tumor cells to proliferate leading to disease recurrence. However, within their study group, there was no difference in disease recurrence in the patients with (28 of 59, 47.5%) or without (75 of 138, 54.3%) peri-operative complications.

Yours sincerely,

Reference

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Response to: Perioperative Morbidity Affects the Long-Term Survival in Patients Following Liver Resection for Colorectal Metastases

Robert Padbury · Marc Schiesser

Received: 6 October 2008 / Accepted: 14 October 2008 / Published online: 4 November 2008

Dear Editor,
Please find our comments to the letter about the article, which was published in the Journal of Gastrointestinal Surgery.

The authors have raised concerns about the methodology used in the analysis:

1. They state that it is not clear whether complications were still a predictive factor in the multivariate analysis when perioperative mortality was excluded. It is correct that we have not addressed this in the paper. In the univariate analysis, perioperative morbidity was a significant prognostic factor whether the perioperative mortality was included or excluded. For the multivariate analysis, we included the perioperative mortality. We did not evaluate the effect of excluding the perioperative mortality on the disease-free survival.
2. The overall survival was affected by perioperative morbidity even when the mortality was excluded (at the least in the univariate analysis). We were trying to investigate whether there was a difference between less severe and more severe complications. There would be a case for analyzing as the authors have suggested and excluding the perioperative mortality.
3. The concept of an extended period of immunosuppression has been raised by another group (Panis et al.[1]), and it was not the aim of the study to investigate this. The primary endpoint was overall survival.

We hope that we could help to clear some of the raised questions and remain with best regards.

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1. Panis Y, Ribeiro J, Chretien Y, Nordlinger B. Dormant liver metastases: an experimental study. Br J Surg 1992;79:221–223.

R. Padbury (✉)
Division of Surgery and Specialty Services,
Flinders Medical Centre,
Adelaide, Australia
e-mail: rob.padbury@flinders.edu.au

M. Schiesser
Department of Visceral and Transplant Surgery,
Universitätsspital Zürich Rämistrasse,
100 8091 Zürich, Switzerland