Physician Competency? Teaching Old Dogs New Tricks

Pierre-Alain Clavien, M.D., Ph.D., David L. Nahrwold, M.D., Nathaniel J. Soper, M.D., Barbara Lee Bass, M.D.

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INTRODUCTION
Pierre-Alain Clavien, M.D., Ph.D.

The public policy committee of the Society for Surgery of the Alimentary Tract (SSAT) held a panel on "Physician Competency" during Digestive Disease Week in New Orleans on May 18, 2004. Developing and assessing physician competencies, particularly surgeon competencies, is a challenge and a subject of many discussions worldwide. The goal of surgical training in any system is to produce competent professionals capable of meeting the health care needs of the society. A surgeon must learn to operate safely and skillfully. The traditional way of teaching has been in the operating room, is based on an exemplary role model, and is monitored through subjective assessments. "See one, do one, teach one" has been the adage of many generations. The operating room is no longer the ideal learning environment because of (a) increasing time constraints, (b) cost, stress, and ethical considerations, (c) hours and shift restrictions for residents, (d) a shift from inpatient to ambulatory surgery, (e) the use of more complex (laparoscopic) procedures, and (f) the public's attention. These constraints have resulted in a shift towards a more objective measurement of outcome and surgeon abilities, and, thereby, decreased interaction between residents and senior role models.

What makes a surgeon competent? Certificates and diplomas are still important testimonies of achievements, but will the future rely on new teaching tools, new routines, and continuous assessments? In this symposium, David Nahrwold attempts to define "What is Competence?" Nat Soper provides insights into "Teaching Old Dogs New Tricks," and finally Barbara Bass covers the topic of "Measuring and Maintaining Competency."

WHAT IS COMPETENCE?
David L. Nahrwold, M.D.

The purpose of this section is to review the genesis of the competence movement in medicine and describe competence as it applies to the medical profession. Previous reviews of this subject have been published elsewhere.[1–4]

Our society is pervaded by a fixation on quality. The business and industrial community recognizes that high-quality products and services are essential to compete in our global economy, using techniques and concepts such as zero defects and six sigma. Accordingly, the public has expectations that providers of services, including mechanics, hairdressers, lawyers, and physicians, will be competent.

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From the Department of Surgery, University Hospital Zurich (P.A.C.), Zurich, Switzerland; Department of Surgery, Feinberg School of Medicine (D.L.N., N.J.S.), Northwestern University, Chicago, Illinois; and Department of Surgery, University of Maryland School of Medicine (B.L.B.), Baltimore, Maryland.
Reprint requests: Pierre-A. Clavien, M.D., Ph.D., University Hospital of Zurich, Department of Visceral and Transplant Surgery, Raemistrasse 100, 8091 Zurich, Switzerland. e-mail: clavien@chir.unizh.ch

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Webster's *New World College Dictionary*[5] defines competence and competent in a typical manner: "com-pe-tence n. Condition or quality of being competent." "com-pe-tent adj. Well qualified; capable; fit (a competent doctor)." Thus, although competence and the competent individual are defined, the competent physician is not.

The public wants competent physicians. Variations in care, poor service, and preventable medical errors have eroded confidence in the competence of physicians in recent years, even to the extent that the professional privilege of self-regulation is endangered. To restore the public trust, physicians must evaluate their competence as a profession and as individual practitioners within the health care system. Individually and as a profession, physicians must provide the public with evidence of their competence.

In the United States, the profession and individual physicians can demonstrate their competence to the public through certification by a specialty board that is a member of the American Board of Medical Specialties (ABMS). Currently, approximately 90% of physicians in the Unites States are certified by at least one ABMS member board. Physicians view their certification as validation of their education and training and confirmation that they possess the requisite knowledge to practice their specialty. Hospitals, insurance companies, and health plans value certification as an indicator of quality, for most require board certification for medical staff or physician panel membership and for awarding clinical privileges. The public has been educated to believe that certification is an important, distinguishing credential for physicians. Thus, certification has earned credibility among physicians, health care organizations, and the public.

ABMS, the umbrella organization for the 24 medical specialty boards, consists of representative of the boards who set standards, share information, and monitor the performance of the boards (Table 1). In the late 1990s, ABMS, although satisfied with the rigor and process of initial certification, began to be concerned that recertification was insufficient evidence that a physician was delivering quality care. Most boards required diplomates to recertify every 10 years by passing an examination. ABMS and its member boards realized that the turnover of much knowledge was faster than every 10 years, and that although an examination measured factual knowledge and some aspects of medical judgment, it was not always relevant to the individual physician's practice. Although an essential element, an examination for medical knowledge does not connote competence or adequately measure the broader range of attributes the public desires in their physicians. In 1998 the ABMS appointed its Task Force on Competence, which attempted to define competence and to change the process of recertification to more adequately measure the characteristics required of contemporary physicians to competently practice their specialties.

Table 1. Member boards of the American Board of Medical Specialties (ABMS)

- Allergy and Immunology
- Anesthesiology
- **Colon and Rectal Surgery**
- Dermatology
- Emergency Medicine
- Family Practice
- Internal Medicine
- Medical Genetics
- **Neurological Surgery**
- Nuclear Medicine
- **Obstetric and Gynecology**
- **Ophthalmology**
- **Orthopedic surgery**
- **Otolaryngology**
- Pathology
- Pediatrics
- Physical Medicine and Rehabilitation
- **Plastic Surgery**
- Preventative Medicine
- Psychiatry and Neurology
- Radiology
- **Surgery**
- **Thoracic Surgery**
- **Urology**

Bold indicates that a surgical board is available.

The task force found that it could not define physician competence, and recognized that no appellation could warrant that a physician was competent at all times for all aspects of his or her practice. Nevertheless, the task force was able to describe the competent physician, and did so as follows: "The competent physician possesses the medical knowledge, judgment, professionalism, and clinical and communications skills to provide high-quality patient care. Patient care encompasses the promotion of health, prevention of disease, and diagnosis, treatment, and management of medical conditions with compassion and respect for patients and their families. Maintenance of competence should be demonstrated throughout the physician's career by evidence of lifelong learning and ongoing improvement of practice." The task force then began to identify the competencies embedded in this description.

Concomitantly, the Accreditation Council on Graduate Medical Education (ACGME) was studying physician competence and obtaining the expertise and

Table 2. Six general competencies according to Accreditation Council on Graduate Medical Education and the American Board of Medical Specialties

1. Medical knowledge
2. Patient care
3. Interpersonal and communication skills
4. Professionalism
5. Practice-based learning and improvement
6. Systems-based practice

opinions of educators, practicing physicians, patients, health care experts, and opinion leaders to determine their expectations of physicians. The ACGME categorized the many desired attributes of physicians into six general competencies that collectively describe the competent, contemporary physician and are embedded in the description of the competent physician (Table 2). Together, the ACGME and the ABMS adopted the six general competencies as attributes that should be taught to residents and should be displayed by residents as well as physicians throughout their careers.

Subsequently, ABMS adopted a new paradigm for the evaluation of practicing physicians, moving from recertification every 10 years to maintenance of certification, in which diplomates will "maintain" their initial certification by ongoing, periodic demonstration of the six general competencies throughout their practicing lives. Diplomates also will be required to meet other requirements of their boards. The maintenance of certification programs of ABMS member boards are designed to help diplomates improve their practices. The improvement paradigm requires the diplomate to accumulate data about his or her performance and to improve it through a variety of learning modalities. It is the expectation of ABMS and its member boards that initial certification and maintenance of certification will serve as an indicator of quality and be accepted as such by organizations that monitor quality of care, health plans, and the public.

TRAINING IN LAPAROSCOPIC SURGERY: "TEACHING OLD DOGS NEW TRICKS"

Nathaniel J. Soper, M.D.

Laparoscopic operations can be broken down into two general types of procedures—basic laparoscopy (e.g., diagnostic laparoscopy, cholecystectomy, and appendectomy), and advanced laparoscopy, which requires two-handed manipulation, alternative viewing angles of the field, as well as suturing and other skills. The "advanced" category includes essentially everything other than the above "basic" procedures. As opposed to the early days of laparoscopic general surgery, residents now are taught basic laparoscopic techniques during their training period.

However, learning minimally invasive surgery (MIS) is different than learning "open" surgery, and MIS training in residency is very uneven.[6] The learning curve for the majority of advanced procedures is greater than the number of cases available in most residencies.[7] Furthermore, it is more difficult as an attending surgeon to "control" residents during performance of MIS. To add to the difficulty of teaching MIS, operating room time is limited and expensive. Furthermore, MIS itself is significantly different than open surgery. A trainee must learn the physiology of the pneumoperitoneum and various techniques to access the abdominal cavity. Using a video screen, vision is monocular with limited depth perception. Furthermore, there is decreased haptic feedback using laparoscopic instrumentation. The long instruments amplify tremor and the image is magnified to 10×. There is also a fulcrum effect whereby the tip of the laparoscopic instrument moves in the opposite direction of its handle. Finally, the fixed access through the trocar limits the degrees of freedom of the instruments.

There are several venues for teaching fundamental laparoscopic skills, such as recreating three-dimensional depth relationships and navigation of instruments in space. These include the animate laboratory, the inanimate laboratory, and the operating room. The animate laboratory employs cadaveric or large animal models for training. These types of models are very expensive and the use of either cadavers or animals may be a sensitive issue in various areas. Inanimate laboratories have been used to good effect. The training devices currently available include so-called video trainers (an opaque box with trocars allowing access to the interior wherein various physical materials can be manipulated in specific exercises) and virtual reality (VR) simulators. VR trainers allow rudimentary manipulation of instruments and tissues. VR trainers are currently somewhat "cartoonish" with suboptimal tissue interactions and haptics, but the simulator quality is improving rapidly. Finally, several procedure-specific rubber models are being developed for use with laparoscopic trainers. The final location for learning minimally invasive surgery is in the operating room—one of Halsted's training tenets was that the operating theater would be the surgeon's classroom. However, it is increasingly difficult to teach technical skills in the operating room because of expense, the limited resource of time in

the operating room, and concerns regarding medical errors caused by novice trainees.

Inanimate laboratory training thus assumes an important role in teaching MIS. Trainees who practice in a video trainer improve their performance of the trainer-specific skills. A plateau seems to be reached after 30 to 35 repetitions, and the least experienced individuals improve the most.[6,8] However, quantifying skills in a video trainer is problematic, generally requiring a proctor to be present if something more than time of performance is to be included in the scoring. Two reports have shown that practice in a video trainer improves in vivo performance by trainees during subsequent laparoscopic cholecystectomy.[6,8]

The group from McGill University has developed the McGill Inanimate System for Training and Evaluation of Laparoscopic Skills (MISTELS) video trainer curriculum and have demonstrated the merit of this system. Six basic skills are scored on time of performance and accuracy. This system has been shown to be highly reliable and reproducible with established construct and predictive validity. Moreover, receiver operator curves have identified passing scores that maximize sensitivity and specificity, both greater than 0.80.[9]

The beneficial influence of training using VR trainers on subsequent laparoscopic procedures has also been reported. Most of the VR simulators incorporate several different exercises, each with tiered levels of difficulty and performance scores based on efficiency, errors, and time of performance. Multiple studies have shown that practicing the VR skills improves the subsequent performance of these same skills. Several studies have reported that VR practice improves in vivo skills during the performance of laparoscopic cholecystectomy in both pigs and humans.[10,11] In one study comparing video trainer and VR simulators for resident training, 77% of the trainees preferred the video trainer to the VR simulator. The reasons given for this preference were the use of real instruments and camera systems, better depth perception, and the presence of haptic feedback, which is absent in the VR system.[10]

Recently, the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) has developed a program entitled Fundamentals of Laparoscopic Surgery (FLS).[12] This is a basic instructional course in the fundamentals of laparoscopic surgery that teaches standardized basic information determined by experts as important.[13] The FLS program uses CD-ROMs for teaching cognitive information and the MISTELS system for training and assessing technical skills. This allows hands-on learning of motor skills and structured examinations to document learning and "competence" of both cognitive knowledge and technical skills. The examinations have been rigorously developed and validated over several years of formulation and reiteration such that the test can withstand "high-stakes" scrutiny. The FLS program has undergone beta testing demonstrating that it has appropriate psychometric properties, satisfactory reliability, initial validity evidence, viable administrative procedures, and the capability of setting appropriate "pass-fail" standards.

MIS training in residency is generally adequate for basic laparoscopy—the mean number of laparoscopic cholecystectomies performed by chief residents graduating in 2002 was 75 (American Board of Surgery data). However, in most programs there is limited experience in advanced laparoscopy. The mean cumulative experience for any advanced procedures (combined) was less than 25. This compares to the assessment by experts that the experience necessary for competency in most advanced procedures is between 15 and 35 per procedure.[7] Furthermore, chief residents generally do not feel adequately trained to perform advanced procedures at the completion of their program.[13] As a result, more than 80 MIS fellowships have now sprung up around the United States with more than 110 training positions available annually. This is the most popular fellowship currently available in the United States.

Only approximately 15% of a surgical career is spent in formal surgical training. Continuing education thus becomes very important and can take the form of either deductive reasoning and self-education or formal continuing medical education (CME) programs. General surgery recently experienced a period of haphazard training during the initial laparoscopic cholecystectomy "revolution" of the early 1990s.[14] At that time, many surgeons adopted laparoscopic techniques with inadequate training, leading to a number of patient injuries that occurred during the "learning curve." In fact, a whole new literature sprang up in general surgery revolving around laparoscopic cholecystectomy–associated bile duct injuries. There were concerns that governmental agencies would determine who could and who could not perform laparoscopic surgery. The American philosopher, George Santayana stated, "Those who cannot remember the past are condemned to repeat it."

Currently, the major needs for retraining of practicing general surgeons in advanced laparoscopic procedures are in the areas of laparoscopic bariatric operations and laparoscopic colectomy (other areas of surgery utilizing minimally invasive technologies are out of the scope of this review). However, it should be noted that the Food and Drug Administration recently mandated that surgeons initiating clinical use of one of the new carotid artery stents be trained on

a simulator prior to clinical experience. The aim of CME training in surgical techniques should be to eliminate the first very steep portion of the learning curve and to allow the surgeon to start clinical experience in the flatter portion of the curve. Surgical education models in the United States primarily revolve around surgical residency and fellowships. Beyond these formal training opportunities, however, there are no nationally coordinated efforts to provide CME training from a procedural standpoint. The model adopted during the initial phase of laparoscopic cholecystectomy was that of 1 to 3 day courses using large animals for training. This same model, or variants using cadaver models, continues to be the mainstay for teaching practicing surgeons new procedures. There are a few programs currently that provide hands-on CME courses followed by preceptoring within the institution of the trainee. Other institutions provide "mini-fellowships" that last anywhere from 1 to 6 weeks to allow the trainee time in the clinic, the laboratory, and in the clinical operating room.

There have been very few published reports that support the efficacy of the current postgraduate training models. The group from the Carolinas Medical Center has shown that adding a period of preceptoring in the trainees' own institution (up to 11 cases) after a hands-on CME course leads to significantly increased adoption rates of both laparoscopic splenectomy and laparoscopic incisional herniorrhaphy, compared to course participation without preceptoring.[15,16] Their data also suggested that surgeons already experienced in advanced laparoscopic procedures prior to taking a 2-day hands-on course teaching a new operation are more likely to adopt the new technique being taught.[16] There are also anecdotal reports of increased adoption rates following a mini-fellowship experience; most of these mini-fellowships are currently teaching the technique of laparoscopic bariatric surgery.

There are numerous roadblocks to training established surgeons in advanced MIS techniques. These include available time (both for the trainer and the trainee) and money (trainee), licensing, privileging, and malpractice issues (trainer and trainee), as well as the lack of sound educational models guiding the procedural training of established surgeons.[17] Certainly, these programs should be based on established principles of training adults and of teaching technical skills (such as those used for teaching musicians).[18,19]

From a personal standpoint I would suggest the following recommendations for "old dogs" desiring to learn "new tricks": The surgeon must decide how important learning the new technique is to him or herself; a weekend CME course is almost certainly not adequate to learn a complex procedure. One's basic skills and two-handed techniques should be optimized; the FLS course may help to improve cognitive and technical skills and to allow comparison of one's skill level to national norms. Mini-fellowships and/or courses plus preceptoring currently seem to provide the best opportunity for effective procedural training. It is probably helpful to train along with a partner or associate to make the initial clinical cases easier to perform. The alternative to formal courses is to hire a fellowship-trained partner and learn from him or her. Certainly, it is imperative not to initiate a clinical program unless or until one feels confident and has had a proctor or preceptor present for at least one case.

In conclusion, surgical residencies are doing a fair job of teaching basic laparoscopic procedures, but are generally inadequate for training advanced laparoscopic procedures. The SAGES FLS program should help assure competency in basic MIS knowledge and skills. MIS fellowships should ultimately provide a supply of trained MIS surgeons; in the meantime, there are established needs for training, particularly for laparoscopic bariatric and colorectal operations. There are numerous hands-on CME courses designed to train practicing surgeons to perform advanced MIS procedures, but there are few data to support the efficacy of these programs. Other procedures and technologies will undoubtedly come along requiring retraining of established surgeons: educators must develop programs to retrain practicing surgeons based on established theories of adult learning and professional technical skills training. These training efforts will likely incorporate new simulator technology in the process.

MAINTENANCE OF CERTIFICATION: DEFINING SURROGATE MEASURES OF COMPETENCY

Barbara Lee Bass, M.D.

As members of a profession, surgeons have a societal obligation to self-regulate and set standards for care. As individual surgeons, we similarly hold a personal obligation to ensure that the care we provide to our patients is based on current surgical knowledge and patient care principles and that the care we provide is properly executed and delivered with autonomy and respect for our patients. The recognition of this professional responsibility was the principle that lead to the creation of certifying boards in American medicine and surgery in the first half of the 20th century. These American boards are unified in setting standards to foster the delivery of high quality health care by ensuring the quality and competency of the physician workforce, as discussed

above. The ABMS (Table 1), which includes 10 surgical boards, is the umbrella organization unifying these medical and surgical boards.

All member boards have set rigorous standards for achieving initial board certification, defining training requirements, practice experience requirements, assessment of professional standing, and rigorous initial examination requirements. The achievement of board certification is a demonstration that a diplomate has met the high standards of a competent provider in a given specially area. For over 50 years, this initial certification process was the only objective assessment of cognitive knowledge and patient care required of practicing surgeons. Recognizing that this initial competence may not be durable over a 40 or 50 year professional lifespan, the member boards of the ABMS initiated a recertification requirement in 1973. Diplomates would thereafter be required to provide evidence of professional standing, continuing education and pass a secure multiple-choice examination once every 10 years. Although many applauded this effort to reassess a diplomate's knowledge, others criticized the recertification process as a minimal measure of a diplomate's professional abilities—his or her actual competence as a physician or surgeon. For general surgeons, the American Board of Surgery (ABS) recertification examination covers material in all of the essential content areas of general surgery training (Table 3). More than 90% of diplomates pass the examination at the 10- and 20-year recertification interval. However, the cohort of diplomates now taking the examination at the 30-year interval pass the examination at a substantially lower rate; 20% to 30% of the examinees fail the exam. Recognizing that most surgeons focus their practices to certain areas within the essential content area, is this comprehensive recertification examination a valid test of knowledge? Are these surgeons in their third decade of practice truly lacking in medical knowledge and patient care skills? Or is the ABS recertification examination too broad in scope? Or does it poorly test their knowledge in their actual areas of practice?

Table 3. Essential content areas of general surgery training

- Alimentary tract
- Abdomen and its contents
- Breast, skin, and soft tissue
- Endocrine system
- Head and neck surgery
- Pediatric surgery
- Surgical critical care
- Surgical oncology
- Trauma/burns
- Vascular surgery

In recent years, public scrutiny of the health care system and of the quality of care provided by physicians and surgeons has increased dramatically. Physician competency has been challenged, albeit perhaps unfairly. Nonetheless, the member boards of the ABMS have taken the opportunities provided by such scrutiny to reassess our own standards for objective appraisal of how we critique our professional activities. In 1999, as a first step in this self-appraisal, the ABMS defined the core components of six competencies (Table 2) to define those aspects of being a physician and surgeon that are essential to high-quality patient care (see first section of this article). Applying metrics to these competencies, however, proved to be more difficult. Hence, the member boards have sought to develop a process that can utilize surrogate measurable criteria to assess objectively evidence of competency in practice on a continuous basis. Crafted over the last 3 years, the Maintenance of Certification (MOC) program was unanimously endorsed by the ABMS in 2002. In MOC all member boards have committed to agree to evolve from periodic recertification programs to MOC programs. The programs are to be initiated in 2005 for all new diplomates and on a rolling basis for diplomates whose certificates are expiring in the old recertification process.

The ABMS has defined four components essential to all MOC programs. Each board must develop criteria to assess (1) professional standing, (2) evidence of lifelong learning and self-assessment, (3) cognitive expertise, and (4) practice performance and assessment. Each member board can stipulate the precise methods to be utilized for each of these four components provided the criteria are consistent with the framework endorsed by the ABMS at large. The ABS has been carefully considering these metrics for the last 2 years. Some of the criteria have been formulated while others remain in evolution. The remainder of this report will summarize the current framework of the MOC program in general surgery of the ABS (from Surgery ABo, maintenance of certification information file). The unresolved issues in each of the four required areas are also being addressed.

Part 1: Assessment of Professional Standing

The ABS will require all diplomates to maintain an unrestricted license to practice medicine; loss of licensing will result in forfeiture of the ABS certificate. Verification of clinical privileges and professional standing will be required from chiefs of surgery or chairs of credentials committees at institutions

where surgeons practice, every 3 years. While these criteria may seem straight forward, application of these requirements may prove challenging for some diplomates. The ABS is considering how to allow surgeons with professional activities restricted to administrative, research, educational, or other activities without clinical privileges to meet this requirement. Should these surgeons maintain active certificates the same way surgeons in practice do? Should the certificate provided to surgeons in these capacities reflect this difference?

Part 2: Demonstration of Lifelong Learning and Self-Assessment

ABS diplomates will be required to complete 50 hours of continuing professional development (CPD) education, 30 of which must be Category 1 each year. Proof of CPD completion will be required every 3 years. Furthermore, diplomates will be required to complete a self-assessment examination every 3 years after certification. The testing tools for this self-assessment are not fully defined. Materials that will meet the requirements include American College of Surgeon programs such as the Surgical Education and Self-Assessment Program, the testing modules in the *Journal of the American College of Surgeons*, and other publications. The ABS is partnering with the American College of Surgeons to inventory materials that could be of value to diplomates in both the self-education and assessment programs. Issues that remain unresolved regarding Part 2 include the scope and content of the CPD and testing. Should diplomates be required to maintain current knowledge in all the essential content areas of general surgery? Should they be allowed to read and test in areas only relevant to their actual practices? Should the ABS craft a modular MOC education and assessment program, allowing diplomates to complete a "core" content area, perhaps covering perioperative management and areas of general surgery essential to the public welfare in the event of national emergency, and then add on modules precisely relevant to their practices? In many respects, the program with greatest public credibility is the latter—patients want their doctors to be knowledgeable in their actual areas of practice, not in areas where they have no clinical activity.

Part 3: Demonstration of Cognitive Expertise

ABS diplomates will be required to take a secure examination once in every 10-year MOC cycle. At the present, the exam is anticipated to be a multiple-choice computer-based examination. As in Part 2, unresolved issues include definition of the scope of the content of the examination—broad or focused, comprehensive or modular—and again the question of truth in labeling with the certificate remains undetermined. Should all certificates look the same, regardless of the examination content?

Part 4: Practice Performance Assessment

For the ABS, the means to assess this requirement remains under discussion. Ideally a method of outcomes assessment that is scientifically and educationally valid will be developed to allow diplomates to review their own practices and in so doing improve the quality of care they practice. The ABS recognizes, however, that measures to assess outcomes of practice remain rudimentary at best. The Veterans Administration National Surgical Quality Improvement Program (NSQIP) is the best developed outcome system; however, even this program allows measurement only of outcomes of surgical services rather than individual surgeons. This program has now been validated in private sector hospitals in an Agency for Healthcare Research and Quality–funded American College of Surgeons sponsored multisite trial, and the ACS–NSQIP Program was opened to enrollment of private sector hospitals around the country in October 2004. One could envision that diplomates practicing in NSQIP hospitals, which have the only risk-adjusted outcomes system in existence, would have access to their own outcomes data and as such their review of these data could meet the MOC program requirements. However, this program is currently available to a very limited number of diplomates. The ABS is considering other programs that diplomates could participate in to meet this requirement, including cooperative groups, surgical society registries, and others.

The ABS, like other ABMS boards, does not wish to hold and review outcomes. In fact, liability aspects of collecting patient and physician outcome data are problematic for ABMS boards and are the topic of ongoing debate. The ABS does, however, desire to create a system that will allow diplomates to participate in outcomes assessment programs to accurately and openly assess the results of their surgery so that areas for improvement can be identified. Although trials of surgeon self-reporting systems in the past have not been successful, possible avenues for self-reporting and benchmarking against standards are being considered. The American College of Surgeons is developing a personal digital assistant–based case reporting system for fellows. Surgeons could enter clinical data on their patients and then subsequently benchmark their own performance on this self-reported data relative to nurse-collected data in the

NSQIP. Although self-reported data would be used, this would serve as a starting point to allow surgeons an opportunity to get a fair appraisal of their own results. Fundamentally believing that our diplomates do wish to provide the highest quality care and do wish to identify areas for improvement in their own practice, this confidential benchmarking program could be a valuable first step in practice assessment. Diplomates who find themselves with outcomes below standard would be stimulated to pursue educational programs to foster improvement in the care they provide.

In summary, the goal of the ABS MOC program is to document and improve the overall quality of the care provided by a surgeon throughout a lifetime of practice. The goal is not to identify the "bad apple" surgeon. The goal is to encourage individual surgeons to commit to lifelong education and scrutiny of their own outcomes, because it is the right thing to do for patients. Surrogate measures for competence developed for the ABS MOC program will need to evolve in the years ahead. The lessons learned from our initial efforts will drive the process and guide us as we establish the systems to continuously improve the self-appraisal systems we as a profession must own.

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Laparoscopic Antireflux Surgery Provides Excellent Results and Quality of Life in Gastroesophageal Reflux Disease Patients With Respiratory Symptoms

Ruxandra Ciovica, M.D., Michael Gadenstätter, M.D., M.Sc., Anton Klingler, Ph.D., Christoph Neumayer, M.D., Gerhard P. Schwab, M.D., M.B.A.

Medical and surgical treatment are able to improve symptoms in patients with gastroesophageal reflux disease (GERD). The aim of this study was to evaluate the outcome following laparoscopic antireflux surgery in GERD patients with primary respiratory-related symptoms and to investigate the quality of life index before and after therapy. Three hundred thirty-eight consecutive patients underwent surgical treatment for GERD-induced symptoms. Of this group 126 patients had primary respiratory symptoms related to GERD. All patients were studied by means of a symptom questionnaire, endoscopy, esophageal manometry, 24-hour esophageal pH monitoring, and a barium esophagogram. In addition, the quality of life was measured by the means of the Gastrointestinal Quality of Life Index (GIQLI). All patients had medical therapy with proton pump inhibitors preoperatively. A laparoscopic fundoplication was performed in all patients. The outcome was assessed 3 and 12 months postoperatively. Following surgery, all respiratory symptoms were significantly improved. While GIQLI was highly impaired before surgical therapy, a significant improvement of quality of life was obtained. Because medical treatment is likely to fail in GERD patients with respiratory symptoms, the need for surgery arises and may be the only successful treatment in the long term. Quality of life was significantly improved by surgical treatment.
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Key words: Gastroesophageal reflux disease, respiratory symptoms, surgery, quality of life

Gastroesophageal reflux disease (GERD) is frequently associated with respiratory symptoms, which are found in up to 25% of GERD patients.[1,2] Several mechanisms for GERD-induced respiratory symptoms (RS) have been discussed. Microaspiration into the lung and stimulation of the vagus nerve by the refluxate are considered to be the two main mechanisms.[3,4] Although the impaired lower esophageal sphincter is the basic anatomic defect, several other factors such as impaired esophageal and antroduodenal motility, delayed gastric emptying, reflux of duodenal juice, alterations of gut neuropeptides, and free radical damage contribute to the development of GERD.[3,5–7] It has been shown that reflux from the stomach and duodenum can reach not only the larynx but also the pharynx, the nose, and the lung.[1] The aim of this study was to evaluate the short- and long-term outcome of GERD-related RS following antireflux surgery and to assess the effect of surgical therapy on quality of life.

MATERIAL AND METHODS

From 2000 to 2003, a group of 338 consecutive GERD patients were operated on in one expert center by two surgeons. One hundred twenty-six patients with GERD-related RS entered this study. The RS consisted of one or a combination of the following: cough, hoarseness, sore throat, laryngitis, bronchitis, and asthma. All patients were examined by a pulmologist to exclude primary diseases of the airways and/or

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From the Department of Surgery, (R.C., M.G., G.P.S.), General Hospital of Krems, Krems, Austria; Department of Surgery (M.G., A.K.), University Hospital of Innsbruck, Innsbruck, Austria; and Department of Surgery (C.N.), University Hospital of Vienna, Vienna, Austria.
Reprint requests: Ruxandra Ciovica, M.D., Department of Surgery, General Hospital of Krems, Mitterweg 10, A-3500 Krems, Austria. e-mail: ruxandraciovica@hotmail.com

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the lungs. Patient evaluation included physical examination, a standardized symptom questionnaire, length of medical acid suppression, chest radiographs, upper gastrointestinal endoscopy, barium swallow esophagogram, esophageal manometry, 24-hour esophageal pH monitoring, and the assessment of a quality of life score.

Standardized biopsy samples were taken from the gastroesophageal junction. Esophagitis was graded using the Savary Miller classification system.[8] Barrett's metaplasia was confirmed by the presence of columnar-type epithelium with intestinal metaplasia in the esophageal biopsy specimen.[9] In addition, laryngeal lesions were inspected carefully regarding presence of inflammation, edema, leukoplakia, or ulcerations.

Esophageal manometry was performed using a stationary pull-through technique with a five-channel water perfused catheter with 5 cm spacing between the channels.[10] Twenty-four-hour esophageal pH monitoring was performed as described previously.[11] A DeMeester score of more than 14.8 indicated abnormal acid reflux. Medication that might interfere with esophageal motor function (i.e., metoclopramide, cisapride, nitrates, β-agonists, and calcium channel–blocking agents), and esomeprazole were discontinued 7 days before both studies. Preoperative barium esophagogram was completed in all patients for assessment of the anatomical situation and to clearly identify hiatal hernias.

Disease-related quality of life was evaluated using the Gastrointestinal Quality of Life Index (GIQLI).[12,13] This questionnaire is well established and validated and has been recommended by the European Study Group for Antireflux Surgery. Based on responses to 36 items, the general score for the GIQLI is graded on a scale from 0 to 144 points. The GIQLI is divided into five subsections: gastrointestinal symptoms (0–76 points), emotional status (0–20 points), physical functions (0–28 points), social functions (0–16 points), and a single item for stress related to medical treatment (0–4 points). The questionnaire was handed to all patients before surgery, 3 months following surgery, and at the time of the final postoperative control. Furthermore, follow-up investigations included clinical assessment and endoscopy with biopsies, esophageal manometry, 24-hour esophageal pH monitoring, and a barium esophagogram performed 3 and 12 months postoperatively.

All patients had medical treatment with proton pump inhibitors before surgery (at least esomeprazole 40 mg daily for 3 months). A higher dose was applied if patients still suffered from GERD symptoms on the standard dose. Antireflux surgery was indicated for inadequate control of symptoms despite maximal conservative treatment or if patients demanded surgery. Based on presurgical evaluation, the Nissen fundoplication was performed in patients with normal esophageal body function, and in the case of impaired esophageal peristalsis a partial posterior fundoplication was performed. Both procedures were completed laparoscopically as previously described.[14,15]

Statistical Analysis

Values are expressed as medians and ranges (manometric parameters and DeMeester score) or mean± standard deviation (quality of life scores). Changes in preoperative versus postoperative general and respiratory symptom rates were evaluated using the McNemar test. If the McNemar test was not applicable due to the lack of two levels for each time point, a binomial test against the preoperative symptom rate was applied. The Wilcoxon test for paired observations was applied for manometric parameters and the DeMeester score; for quality of life scores, paired t tests were used. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

GERD was confirmed to be the reason for RS in all 126 patients. There were 65 male and 61 female patients with a median age of 52 years (range, 22–74 years). All patients had a positive history of heartburn, and 103 (82%) suffered from intermittent or permanent regurgitation for a median duration of 5 years (range, 2.5–10 years). In addition, 15 patients (12%) complained of dysphagia. The complete list of typical and general GERD symptoms preoperatively and postoperatively is shown in Table 1. All patients were either on long-term esomeprazole 40 mg daily for a median period of 12 months or had been given a trial of esomeprazole therapy for at least 3 months even when medical therapy was not successful. If patients still suffered from GERD-induced symptoms while being on medication, a higher dose (60–80 mg) was prescribed.

Based on endoscopic and radiologic examinations, 116 patients (92%) showed a hiatal hernia with a median size of 5 cm (range, 2–15 cm). A typical Barrett lesion was detected on endoscopy in 35 patients (28%) and was confirmed by histologic examination. Typical preoperative and postoperative manometric and pH monitoring data are shown in Table 2. The Nissen fundoplication was performed in 113 patients (90%) with normal esophageal peristalsis, and the partial posterior fundoplication was completed in

Table 1. Spectrum of general symptoms before and after surgery

General Symptoms	Preoperative, n (%) (n = 126)	3-Month postoperative, n (%) (n = 117)	12-Month postoperative, n (%) (n = 83)
Heartburn	126 (100)	5 (4)†	11 (13)†
Epigastric pain	118 (94)	3 (3)*	2 (2)*
Regurgitation	103 (82)	1 (1)*	1 (1)*
Dysphagia	15 (12)	7 (6)	3 (4)
Globus sensation	20 (16)	4 (3)*	5 (6)
Flatulence	27 (21)	32 (27)	22 (27)*
Vomiting	21 (17)	6 (5)*	0 (0)†
Bleeding episodes	2 (2)	0 (0)	0 (0)

*$P < 0.05$ versus preoperative (McNemar test).
†$P < 0.05$ versus preoperative symptom rate (binomial test).

13 patients (10%) with impaired esophageal body function.

Following surgery, RS were improved significantly. This improvement was permanent. The variety of different RS before and after surgical treatment is shown in Table 3. There was a dramatic decrease in physician visits and hospital admissions for respiratory problems. Patients without RS 12 months following surgery (92%) did not need any specific respiratory medication and could be released from continuous pulmologic controls. Those patients who still suffered from (occasional) RS are in permanent yearly surveillance by our surgical and/or pulmologic department.

Before surgery, GIQLI was significantly impaired compared with normative data and was below the quality of life index of patients with malignant or heart diseases. Following surgery GIQLI was normalized in all subsections, corresponding to a mean intra-individual overall change of 33.3 points ($P < 0.0001$, Table 4). There was no statistical difference between the normal population and the operated patients.

Table 2. Manometric parameters of the Lower Esophageal Sphincter (LES) and the DeMeester reflux score of all patients preoperatively and 12 months postoperatively

	Preoperative	Postoperative
LES resting pressure (mm Hg)	4.5 (0.3 to 21.2)	16.1 (3.3 to 28.4)*
LES intra-abdominal length (cm)	1.0 (0.0 to 4.0)	2.2 (0.0 to 3.8)*
DeMeester score	26.6 (2.2 to 221.9)	3.4 (0.3 to 64.2)*

Values expressed as median and range.
*$P < 0.05$ versus preoperative (Wilcoxon test for paired observations).

DISCUSSION

International studies have reported that up to 25% of the Western population have symptoms of GERD at least once a month and that 4%–7% have daily symptoms.[16] Many mechanisms have been proposed in the pathogenesis of reflux that involve the respiratory tract.[4,16,17] Acute esophagitis with subsequent submucosal edema, the loss of muscle fibers, the increase of submucosal collagen due to the chronic inflammation, and dysplastic changes are supposed to cause an impaired esophageal peristalsis leading to microaspiration of the refluxate.[3] A vagally mediated reflex mechanism is supported by the fact that bronchoconstriction occurs following reflux of acid into the lower esophageal sphincter.[16] Formation of scars or hyperkeratosis of the larynx is followed by glottic and/or laryngeal stenosis, and laryngospasm is an important factor in the development of carcinoma of the laryngopharynx.[18] The reported prevalence of RS in GERD patients ranges from 9% to 50%.[19–21] This suggests that the frequency of dual pathology is

Table 3. Spectrum of respiratory symptoms before and after surgery

Respiratory symptoms	Preoperative, n (%)	3-Month postoperative, n (%)	12-Month postoperative, n (%)
Any symptoms	126 (100)	9 (8)†	7 (8)†
Cough	94 (75)	3 (3)*	3(4)*
Sore throat	58 (46)	5 (4)*	6 (7)*
Hoarseness	54 (43)	5 (4)*	3 (4)*
Laryngeal symptoms	32 (25)	2 (2)*	2 (2)*
Bronchitis	19 (15)	3 (3)*	0 (0)†
Asthma	15 (12)	4 (3)*	1 (1)*

*$P < 0.05$ versus preoperative (McNemar test).
†$P < 0.05$ versus preoperative symptom rate (binomial test).

Table 4. Quality of life scores in normal population, before and after surgery

Score	Normal population	Preoperative	3-Month postoperative	12-Month postoperative
Gastrointestinal Quality of Life Index	122.6 ± 8.5	86.4 ± 19.8†	113.7 ± 20.0*	118.6 ± 19.8*
Gastrointestinal symptoms	62.0 ± 6.3	46.8 ± 11.1†	58.1 ± 10.6*	60.3 ± 10.5*
Emotional status	18.5 ± 2.2	10.6 ± 4.1†	15.9 ± 3.8*	17.0 ± 3.6*
Physical status	23.5 ± 3.1	13.2 ± 4.2†	19.1 ± 4.7*	19.4 ± 4.5*
Social function	14.8 ± 1.8	11.5 ± 3.2†	14.1 ± 2.5*	14.0 ± 2.7*
Stress	3.8 ± 0.1	2.6 ± 1.3†	3.3 ± 1.1*	3.7 ± 0.7*

Values expressed in mean ± SD.
*$P < 0.05$ versus preoperative score (paired t test).
†$P < 0.05$ versus normal population (paired t test).

higher than expected. In our study we identified RS in 37% of 338 patients with GERD; 80% of patients had increased esophageal acid exposure on 24-hour pH monitoring.

It is without doubt that medical therapy has little effect on RS, although it effectively controls heartburn and acute esophagitis.[20,22] This may be due to the fact that antireflux medication with proton pump inhibitors (PPIs) mainly decreases acid production and reflux, neutralizes acid refluxate, and promotes esophageal clearance. Antireflux surgery inhibits the reflux of all gastric and duodenal contents and therefore prevents microaspiration and vagus nerve stimulation, which are both factors that play an important role in the development of GERD-induced RS.[3] This fact is supported by a dramatic clinical improvement of RS in up to 83% and simultaneous reduction of respiratory medication use (corticosteroids, bronchodilators) at least in 78% of patients.[19,23–25]

According to these results, surgical reestablishment of an effective antireflux barrier is essential for the outcome of GERD patients with RS.[20] The potential advantages of antireflux surgery are the reduction of esophageal acid exposure, restoration of the function of lower esophageal sphincter, the improvement of impaired esophageal peristalsis, and the increase in gastric emptying speed.[3]

Our study emphasizes that tailored antireflux surgery is superior to medical treatment regarding reflux-induced RS. Patients achieve excellent long-term outcome following surgery. The quality of life can be increased to a level comparable with the normal population.

CONCLUSION

Several theories confirm the relationship between GERD and RS. Treatment of reflux-associated RS is challenging. Diagnostic evaluation with manometry and 24-hour pH study has emerged as the key test to establish the evidence of a cause-effect relationship and are useful in predicting the outcome of therapy. With increasing severity of the disease, medical therapy is more likely to fail and the need for surgical treatment arises.

Laparoscopic antireflux surgery is able to significantly improve RS, allowing discontinuation of PPIs, systemic corticosteroids, and bronchodilators in most patients and offering the benefit of reduced morbidity. The key question to the surgeon is which patients are best served by operative management to achieve a permanent high quality of life.

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Hepatitis Status, Child-Pugh Classification, and Serum AFP Levels Predict Survival in Patients Treated With Transarterial Embolization for Unresectable Hepatocellular Carcinoma

Trevor W. Reichman, M.D., Ph.D., Phil Bahramipour, M.D., Alison Barone, M.D., Baburao Koneru, M.D., Adrian Fisher, M.D., Daniel Contractor, M.D., Dorian Wilson, M.D., Andrew Dela Torre, M.D., Kyunghee C. Cho, M.D., Arun Samanta, M.D., Lawrence E. Harrison, M.D.

Hepatocellular carcinoma (HCC) represents one of the most prevalent cancers worldwide. Most patients are not surgical candidates, and transarterial embolization (TAE) has been used to treat patients with unresectable HCC. The purpose of this study was to identify factors that predict survival in patients treated with TAE at a Western medical center. Review of a prospective database identified 345 patients treated for HCC at University Hospital (Newark, NJ) between July 1998 and July 2004. Of these patients, 109 patients underwent TAE. Eleven of these patients were subsequently treated surgically and excluded from this study. Of the remaining 98 patients, demographic data and laboratory values were analyzed to predict survival by univariate and multivariate analysis. Several factors, including hepatitis status, Child-Pugh classification, serum alpha fetoprotein levels <500 ng/ml, bilirubin <2.0 mg/dl, prothrombin time <16 seconds, platelet count $<200 \times 10^9$/l, albumin >3.5 gm/dl, and multiple treatments, predicted survival by univariate analysis. Serum alpha fetoprotein levels, Child-Pugh classification, and hepatitis status were found by multivariate analysis to independently predict survival. These factors may help to select patients with unresectable HCC who might benefit from TAE. (J GASTROINTEST SURG 2005;9:638–645)

KEY WORDS: Hepatocellular carcinoma, embolization, alpha fetoprotein

INTRODUCTION

Hepatocellular carcinoma (HCC) represents one of the most common cancers worldwide. Its incidence is highest in sub-Saharan Africa and Southeast Asia, but the number of reported cases of HCC has been steadily increasing in the United States and Europe.[1] The only known curative treatment for HCC is surgical resection or orthotopic liver transplantation. Unfortunately, many patients are not candidates for surgical resection, and efforts have been made to develop alternative therapies to treat unresectable HCC.[2] Systemic chemotherapy has offered dismal results in treating patients with HCC, achieving only 20% response rates with no appreciable survival benefit.[3,4] Recent strategies have focused on regional hepatic approaches, including interstitial therapies (percutaneous ethanol injection, radiofrequency ablation, and cryoablation) and intravascular techniques such as transarterial embolization.

Transarterial embolization (TAE), with or without chemotherapy, provides radiologic response rates ranging from 16% to 62% of patients with unresectable HCC.[5] However, it is uncertain whether this

From the Departments of Surgery (T.W.R., B.K., A.F., D.W., A.D.T., A.S., L.E.H.) and Radiology (P.B., A.B., D.C., K.C.C.), UMDNJ–New Jersey Medical School, Newark, New Jersey.
Reprint requests: Lawrence E. Harrison, M.D., Department of Surgery, Division of Surgical Oncology, UMDNJ–New Jersey Medical School, 185 South Orange Avenue, MSB G524, Newark, NJ 07103. e-mail: L.Harrison@umdnj.edu

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tumor response translates into a survival benefit for these patients. Multiple randomized prospective trials have not demonstrated any survival benefit for TAE when compared to best supportive care.[6–10] However, two recent randomized trials have demonstrated a survival advantage in select patients with unresectable HCC, suggesting that certain subgroups of patients with unresectable HCC may indeed benefit from TAE.[11,12]

In an attempt to identify this subset of patients, several groups have reported predictive factors for survival in patients treated with TAE.[13–15] However, many of these studies were performed at Eastern medical centers whose patient populations are vastly different from the patient populations treated in the United States.[16] The purpose of this study was to identify factors that predict survival in patients treated with TAE at a Western medical center.

PATIENTS AND METHODS

Study Population

A retrospective review of a prospective gastrointestinal malignancy database at University Hospital (Newark, NJ) between July 1998 and July 2004 identified 345 patients diagnosed with HCC. Of these 345 patients, 109 patients underwent TAE. Criteria for TAE included significant hepatic parenchymal dysfunction precluding initial hepatic resection, lesions >5 cm, and lesions <5 cm that were unapproachable for percutaneous ethanol injection or radiofrequency ablation. After treatment, 11 of these patients underwent surgical treatment (10 transplant, one resection), and these patients were eliminated from analysis. Of the remaining 98 patients, demographic data, tumor factors, treatment variables, and laboratory values were analyzed to predict overall survival.

Selective superior mesenteric and common hepatic arteriography was performed via a femoral catheterization with a 5 F angiography catheter to map the arterial anatomy, assess portal flow, and identify the tumor blush. A mixture of polyvinyl alcohol particles (250–350 μm size) and contrast medium was selectively injected into the blood vessels supplying the tumor. A postembolization angiogram was performed to demonstrate complete absence of tumor vascular enhancement. Patients undergoing TAE with intra-arterial chemotherapy (TACE) received 10 mg mitomycin and 30 mg of doxorubicin mixed with the polyvinyl alcohol particles. To decrease postprocedure hepatic failure, patients with poor parenchymal reserve (Child's class C) underwent multiple partial ablations. The decision to perform TACE versus TAE was not randomized and was at the discretion of the responsible physician. Serum AFP levels and radiologic imaging were obtained 3 to 5 weeks after each TAE.

Statistical Analysis

Continuous variables are presented as median (range). All demographic data, laboratory values, and pathology data were analyzed as predictors of survival by univariate and multivariate analysis. *P* values were calculated using either χ^2 test or Fisher exact test where appropriate. A *P* value of ≤ 0.05 was considered to be significant. Values found significant by univariate analysis were further analyzed by multiple regression analysis using the SPSS statistical program

Table 1. Patient demographics and treatment characteristics

	n
Sex	
Male	76
Female	22
Race	
White	35
Hispanic	8
Black	22
Asian	8
Unknown/other	25
Chronic alcohol ingestion	
Yes	26
No	51
Unknown	21
Hepatitis	
B	16
C	37
B and C	4
None	26
Unknown	15
Child-Pugh classification	
A	32
B	24
C	14
None	10
Unknown	18
Number of lesions	
1	52
2	15
3	5
≥4	15
Unknown	11
Treatment	
Single embolization	62
Multiple embolizations	36
Chemotherapy	
No	37
Yes	61

(SPSS, Inc., Chicago, IL). Survival was also analyzed by method of Kaplan-Meier, and curves were compared using the Cox-Mantel log-rank test.

RESULTS

The demographic and treatment data of patients with unresectable HCC treated with TAE are summarized in Table 1. Of the 98 patients, 76 were male and 22 female, and the median age was 65 years (range 26–87 years). The racial distribution was white (36%), Hispanic (8%), African American (22%), and Asian (8%); 24% were other or unknown. Median follow-up time was 18 months (range 2–57 months). Of the 98 patients, 10 were lost to follow-up. The median overall survival of the population was 10.4 months, with a 5-year survival of 31%. Of the 98 patients, 57 had hepatitis B and/or C as determined by routine serology, and 27% of patients admitted to chronic ethanol ingestion. The diagnosis of cirrhosis was determined by a combination of radiologic criteria (liver contour and size, presence of varices, ascites) and serum liver parenchymal function tests, including serum bilirubin, albumin levels, international normalized ratio, and prothrombin time. Hepatic parenchymal function was assessed by the Child-Turcotte-Pugh class system and, of those patients with documented cirrhosis, 33% presented as class A, 24% as class B, and 14% as class C. The remaining patients (29%) did not have documented cirrhosis. Most patients presented with a single lesion (n = 52).

In an attempt to identify factors predictive of survival in this set of patients, demographic and laboratory data were evaluated by univariate analysis (Table 2). Child's class A and B ($P < 0.02$), serum alpha fetoprotein (AFP) <500 ng/ml ($P < 0.01$), bilirubin <2 mg/dl ($P < 0.007$), prothrombin time <16 seconds ($P < 0.04$), platelet count $<200 \times 10^9$/l ($P < 0.04$), albumin concentration >3.5 gm/dl ($P < 0.02$), and more than one embolization ($P < 0.007$) were all found to be positive predictors of survival. No significant difference was found between patients treated with TAE versus patients treated with TACE ($P = 0.3$) (Fig. 1).

By multivariate analysis, serum AFP levels ($P = 0.03$), Child-Pugh classification ($P = 0.02$) and

Table 2. Factors predicting survival

	n	Median survival (mo)	5-year survival	Univariate	Multivariate
Hepatitis					
Negative	26	8.4	21%	0.009	0.03
Positive	57	23.3	40%		
Child's					
A, B or none	66	NR	50%	0.02	0.02
C	14	5.7	24%		
AFP (ng/ml)					
<500	64	23.3	39%	0.01	0.03
⩾500	34	8.4	32%		
Bilirubin					
>2.0	18	9.5	0%	0.007	NS
<2.0	65	NR	60%		
Tumor size (cm)					
<3	40	NR	77%	0.01	NS
⩾3	49	18.1	47%		
PT					
<16	72	15.7	33%	0.04	NS
>16	12	9.5	9.5%		
Platelet count					
>200	27	8.9	0%	0.04	NS
<200	66	23.3	41%		
Albumin					
>3.5	53	8.9	38%	0.02	NS
<3.5	40	15.7	23%		
Treatment number					
1	62	8.9	40%	0.007	NS
>1	36	23.3	39%		

NR = not reached.

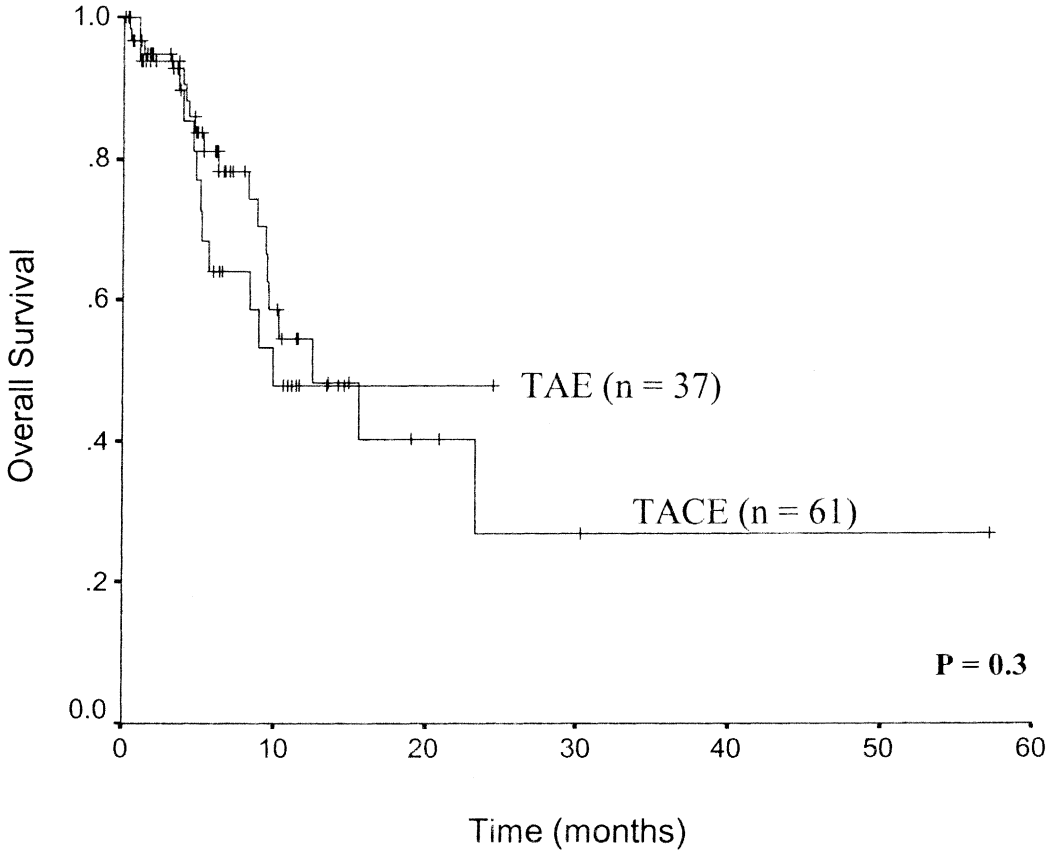

Fig. 1. Overall survival comparing patients undergoing transarterial embolization (TAE) versus transarterial chemoembolization (TACE)

hepatitis status ($P = 0.03$) were found to independently predict survival (Table 2). Elevated serum AFP levels (⩾500 ng/dl) also predicted a worse survival (median survival = 8.4 months) compared to patients with serum AFP levels <500 ng/dl (median survival = 23.3 months, $P = 0.03$; Fig. 2). The 5-year survival of patients classified with Child's class C cirrhosis was 24% (median survival = 5.7 months) versus 50% for patients with Child-Pugh class A or B (median survival not reached, $P = 0.02$, Fig. 3). In addition to serum AFP levels and Child-Pugh class A and B, the presence of hepatitis (B and/or C) also predicted a significantly prolonged survival by multivariate analysis ($P < 0.03$). The median survival of patients with a positive hepatitis status was 23.3 months with a 5-year survival of 40%. In comparison, patients with no evidence of hepatitis had a median survival of 8.4 months with a 21% 5-year survival (Fig. 4).

DISCUSSION

TAE has been studied worldwide as a possible treatment for unresectable hepatocellular carcinoma, and the results of several studies appear promising. However, the few randomized controlled studies published show conflicting results; some trials showed improved survival with treatment[11,12] while others demonstrated no survival benefit.[6–10] These results suggest that only a select group of patients may benefit from TAE. Despite its frequent use as a treatment for unresectable HCC, few studies involving patients from U.S. medical centers have identified prognostic factors that allow selection of patients who may benefit from TAE. In this study, we identify several prognostic factors, including AFP level, Child-Pugh classification, and positive hepatitis status, that predict enhanced survival in patients treated with TAE.

Benefit from treatment with TAE appears limited to patients with hepatic parenchymal reserve. Several studies have reported that numerous factors indicative of liver failure often predict poor outcome in TAE patients.[14,15,17,18] Our study confirmed that several factors measuring liver function, including Child-Pugh classification, bilirubin, PT, and albumin levels, predicted survival by univariate analysis. It is not surprising that patients with poor liver function fair less well then patients with normal or slightly impaired

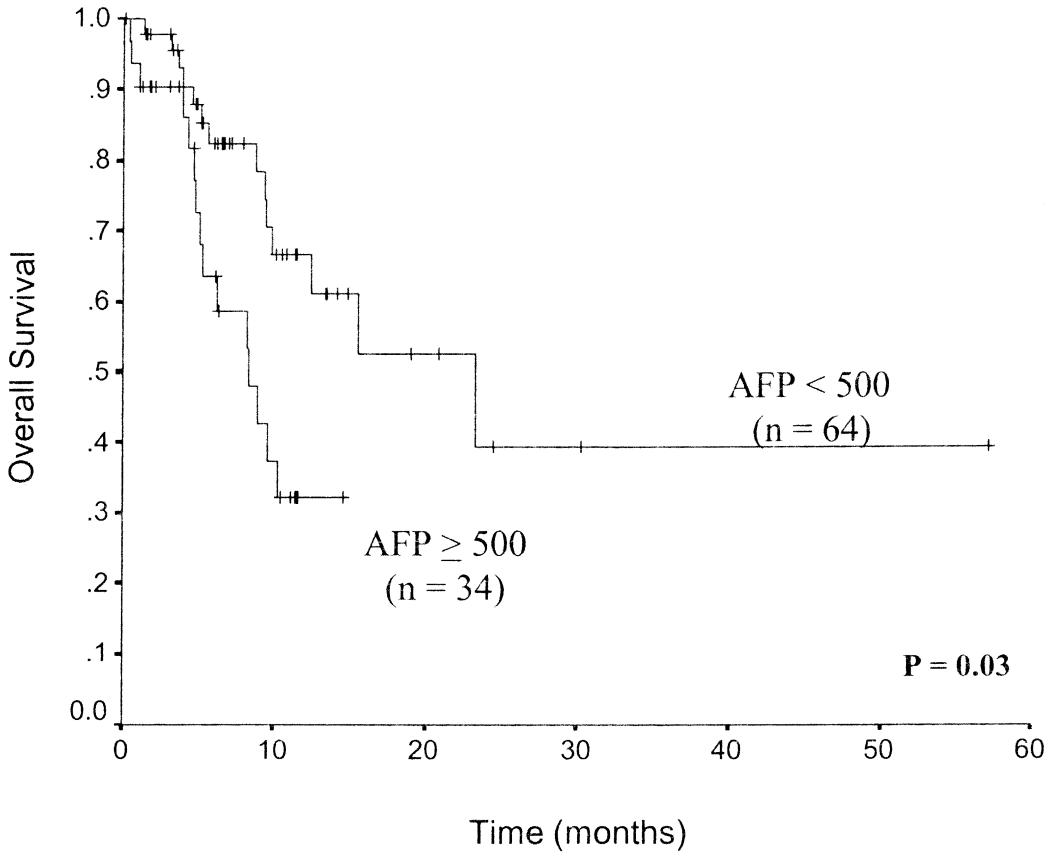

Fig. 2. Overall survival by serum AFP level. Patients with initial serum AFP levels >500ng/ml had a significantly worse survival compared to those with levels ≤500 ng/ml.

function. Liver failure is often reported as one of the complications of TAE, indicating some residual liver function is required to tolerate the associated hypoxic insult and hepatic necrosis that occurs during embolization.[17] Based on our data and that of others, patients with severe parenchymal dysfunction (Child's class C) may not be appropriate candidates for TAE. Serum AFP levels have been shown to correlate with poorer prognosis in a variety of patients treated for HCC.[19–21] We noted that patients with a serum AFP level >500 ng/ml had a reduced 5-year survival compared to patients with lower AFP levels. O'Suilleabhain et al. also reported that an elevated serum AFP level (>1000 ng/ml) independently predicted 5-year survival in patients undergoing TACE for unresectable HCC.[14] Despite the variable thresholds, serum AFP level is consistently reported as a predictive factor for survival in patients with HCC and may represent a surrogate marker for either tumor bulk or aggressive tumor biology.

The addition of chemotherapeutic agents as part of the standard embolization protocol has also been tested in several studies. In theory, TACE provides high doses of chemotherapy locally to the tumor, avoiding the toxic side effects of systemic treatment. The addition of chemotherapeutic agents to TAE clearly appears to increase the degree of tumor necrosis.[22] However, based on the few studies comparing TAE and TACE, the effects are controversial, and studies suggest no survival advantage for patients treated with TACE.[23,24] Surprisingly, in a study by Chang et al. in which the chemotherapeutic agent cisplatin was used, the data suggested that patients in the TACE group did worse then those treated with TAE alone, with a 1-year survival of 52.5% versus 72.5%, respectively. However, these results did not reach statistical significance.[23] Our study confirmed these previous findings and indicated no survival advantage for patients treated with TACE. However, caution must be used in interpreting our results since the choice to perform TACE was practitioner-dependent and not randomized. Further trials utilizing novel chemotherapeutic regimens may be more successful.

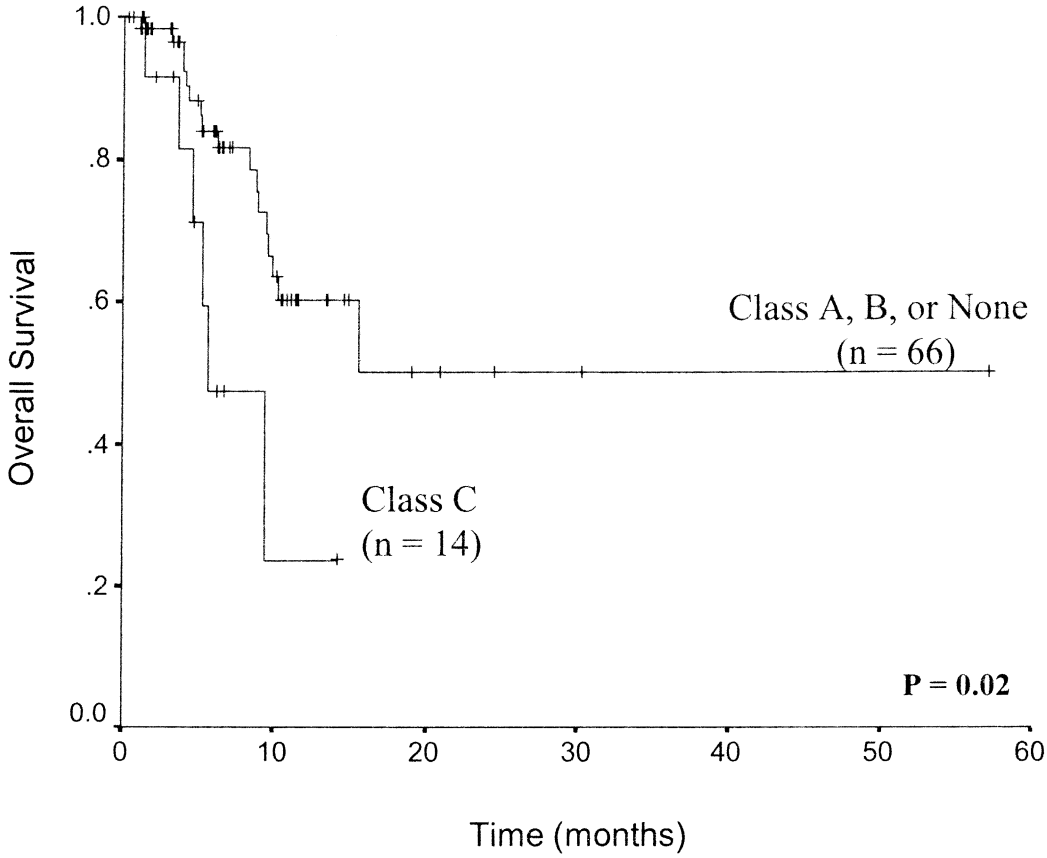

Fig. 3. Overall survival by Child-Pugh class.

Perhaps the most surprising aspect of this study is the finding that patients with hepatitis B and/or C have a better prognosis compared to patients without evidence of hepatitis infection after TAE. It is possible that this is the result of more aggressive screening for HCC in patients with a diagnosis of viral hepatitis, and therefore cancer was recognized and treated earlier in this group. However, this seems unlikely because all patients in the study had unresectable tumors, with no differences in tumor size, number, or serum AFP levels (data not shown). It is also possible that the virus itself has some antitumor effect or that the virus enhances the immunologic response against HCC, impeding tumor progression. In addition, the virus and certain viral products have pro-apoptotic effects on cells.[25] It is possible that a balance exists between carcinogenesis and the pro-apoptotic effects of the virus and that the stress inflicted on cells following TAE treatment may alter this balance and favor an apoptotic pathway. If this balance exists, it would be interesting to determine which factors favor each of these processes and could provide attractive therapeutic targets for patients with both diseases. Biological differences between the tumors derived from hepatitis-infected liver versus tumors in uninfected liver could also account for the differences in survival. The genetic alterations required for hepatocyte transformation are most likely unique between the two groups and therefore the tumors may respond differently to TAE. This hypothesis is supported by the recent report showing differences in gene expression among tumors derived from HCC in patients with hepatitis versus HCC in uninfected patients by proteomic analysis.[26]

Advances in treatments for unresectable HCC are clearly necessary given that most patients are deemed unresectable by surgical criteria. Several studies show a clear survival advantage for patients treated with TAE, especially those patients without evidence of severe hepatic impairment. In this study, we identified several useful markers that may help select and predict patients who might benefit maximally from treatment with TAE. This study also identified an unsuspecting role for hepatitis in prolonging the survival of our patients treated with TAE. Future studies

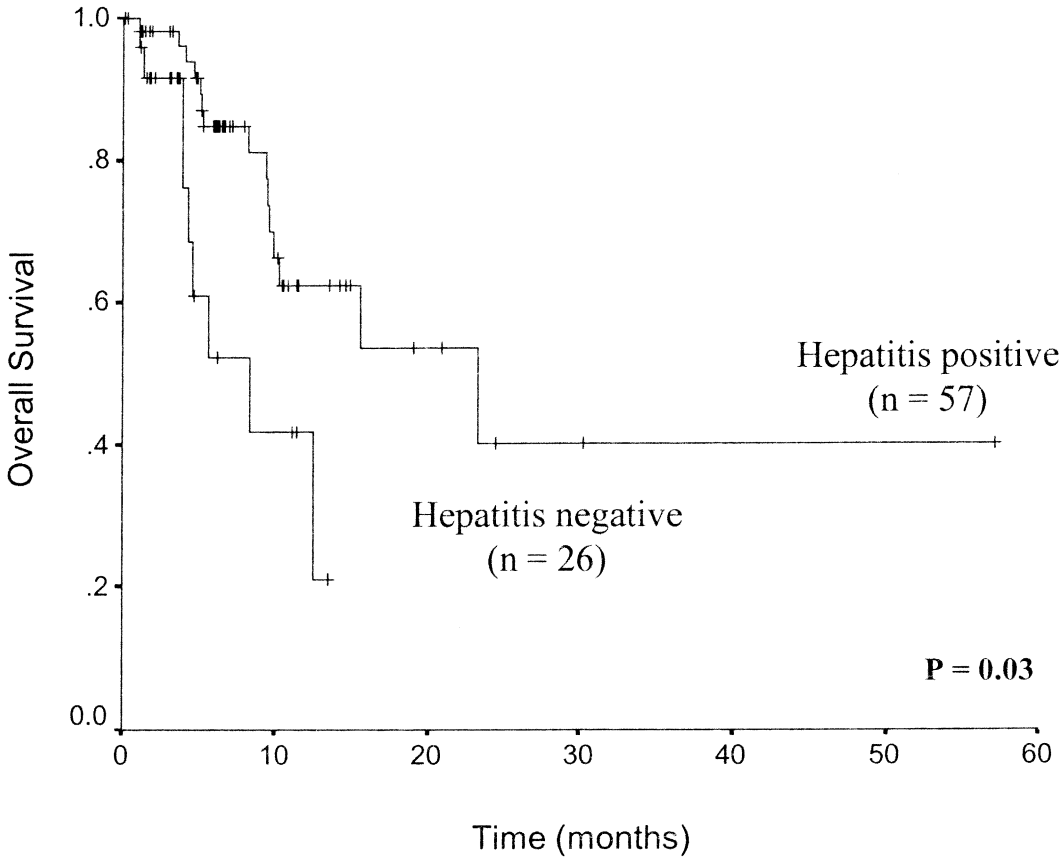

Fig. 4. Overall survival by hepatitis status. Patients with hepatitis B, C, or both had a better survival than those patients with negative hepatitis serology.

should be aimed at addressing the role of hepatitis in HCC progression.

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Right Portal Vein Thrombosis After Splenectomy for Trauma

Mattia Stella, M.D., Alberto Serventi, M.D., Daniele Friedman, M.D.

Portal vein thrombosis may complicate splenectomy in patients with hemolytic anemia and myeloproliferative disease, whereas the frequency of portal vein thrombosis in case of trauma is not defined. A case of right portal vein thrombosis after splenectomy for trauma is reported in this paper. Hematologic workup did not reveal an underlying platelet or coagulation disorder. The patient was promptly anticoagulated with complete recanalization of the portal vein. We conclude that mild symptoms, like abdominal pain and fever, after splenectomy should be investigated with a color Doppler ultrasonography to confirm or rule out a diagnosis of portal thrombosis and to anticoagulate the patient with thrombosis, thus preventing bowel infarction and secondary portal hypertension. Routine postoperative color Doppler might also be justified in all postsplenectomy patients (without hematologic diseases) for early detection of a portal vein thrombosis. (J GASTROINTEST SURG 2005;9:646–647)

KEY WORDS: Splenectomy, portal thrombosis, trauma

Portal vein thrombosis (PVT) is a potentially life-threatening complication following splenectomy. It usually occurs when operation is performed in patients with hematologic diseases,[1] whereas it is a rare event after a surgical procedure for trauma. A case of right PVT following splenectomy for trauma is reported here.

CASE REPORT

A 35-year-old man was admitted to our department for a blunt abdominal trauma following an automobile accident. On physical examination, the patient presented with abdominal tenderness and hemodynamic instability (systolic blood pressure of 80 mm Hg). Hemoglobin at admission was 9.5 g/dl, and a computed tomography (CT) scan showed perisplenic fluid collection and a splenic line of fracture reaching the splenic hilum. There also was a fracture of the eighth left rib. The patient underwent splenectomy through a xiphoumbilical incision; he did not require blood transfusion. The patient did well until postoperative day 11, when he had a fever and mild pain in the right hypocondrium. Hemoglobin was 13.5 g/dl, platelet count was 498,000 cells/mm^3, and both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated (AST, 223 UI/L; ALT, 227 UI/L). A color Doppler ultrasonography (US) showed flow reduction in the right portal vein branch. CT scan displayed absence of contrast diffusion in the right portal vein and hypoperfusion of the right liver (Fig. 1). These findings were consistent with a diagnosis of right PVT.

Hematologic workup did not reveal any disease affecting platelet and coagulation function. The patient was first anticoagulated with intravenous heparin (25,000 UI daily) for 15 days; then Coumadin (warfarin; 5 mg daily) was administered for 3 months. Overall, the hospital stay was 30 days, after which the patient was discharged in a state of well-being.

CT scan performed at 3 months after discharge showed portal recanalization with regular venous perfusion of the right liver (Fig. 2). The platelet count was 850,000 platelets/mm^3, and liver function test results were normal. Coumadin was then stopped, and aspirin (150 mg daily) administration was started.

At 2 years after the event, the patient has no symptoms or laboratory or radiologic findings related to the previous PVT.

DISCUSSION

The global frequency of PVT postsplenectomy may vary from 0.87% to 8% in the different series

From the Department of Surgery, School of Medicine (DICMI), Genoa, Italy.
Reprint requests: Mattia Stella, M.D., Department of Surgery, DICMI (segreteria 3° piano), Largo Rosanna Benzi 8, 16132 Genova, Italy. e-mail: stellam72@hotmail.com

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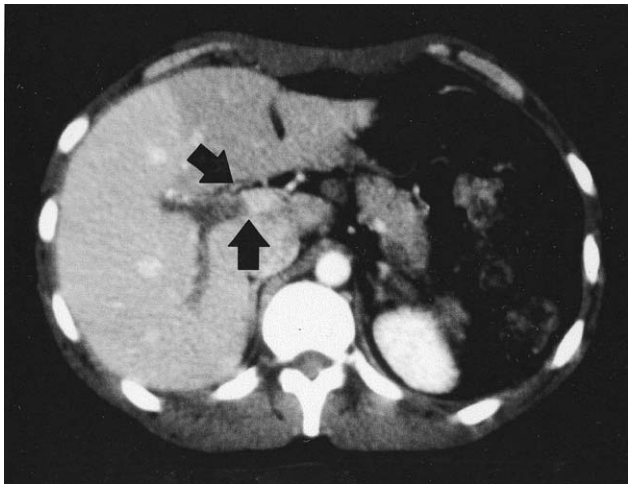

Fig. 1. Computed tomography scan displays a complete thrombosis of the right portal vein (*arrows*) and hypoperfusion of the right liver.

and is up to 40% in patients operated on with myeloproliferative disorders.[1,2] The incidence of PVT in patients with splenectomy for trauma is not well defined.[3]

Van't Riet et al[4] reported no occurrences of PVT among 122 patients who underwent splenectomy for trauma in a series of 563 splenectomies, but the frequency could be underestimated because of the presence of asymptomatic PVT.[1]

PVT may result from local and general factors. The main local factors are splenomegaly, the intraoperative manipulation of the vessels and stasis of blood in the splenic vein stump.[2,4,5] A hypercoagulable state (protein C, protein S, and antithrombin III deficiency) has been advocated as a general factor.[5] Hypercoagulability after a traumatic event could be caused by trauma-induced release of cytokines, which activate the attraction of the platelets and the coagulation pathways.[3] Postsplenectomy thrombocytosis may also play a role in the pathogenesis of PVT, but it is not clearly defined.[1,5]

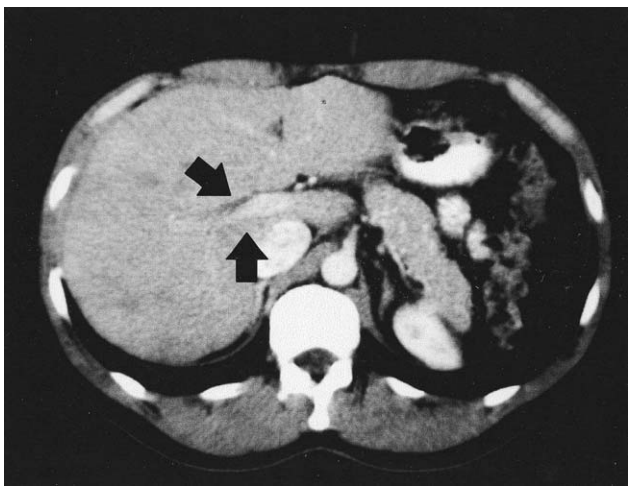

Fig. 2. Computed tomography scan performed 3 months after the onset of right portal venous thrombosis shows recanalization of the right portal vein (*arrows*) and normal liver perfusion.

In the present case, the platelet count was not so high that the development of a PVT would be clearly expected. The mean interval between splenectomy and the diagnosis of PVT is 11.8–12.5 days, although a 9-year interval has also been reported.[1,2]

The symptoms of PVT may be minimal and insidious and include fever, vomiting, abdominal pain, and diarrhea as expression of bowel damage.[1]

Color Doppler US and contrast-enhanced CT scan represent the imaging techniques of choice to detect PVT. An aggressive anticoagulation treatment is aimed at preventing the extension of the thrombosis and bowel infarction. Recanalization of the portal vein occurs in 90% of cases.[2,4]

In the reported case, the diagnosis was made when thrombosis was limited to the right hepatic portal venous branch. Anticoagulation therapy presumably avoided the extension of the clot to the main portal vein, allowing a complete resolution of the PVT. Routine postoperative Doppler US performed for high-risk patients (i.e., patients with hematologic disease) has been proposed to achieve early diagnosis of PVT.[4,5]

Like other authors, we believe that the onset of symptoms, such as fever and mild abdominal pain, after splenectomy should be considered as possibly resulting from an underlying PVT. Prompt anticoagulation is the key treatment to allow portal recanalization and prevent the extension of the thrombosis, damage to the bowel, and the onset of a secondary portal hypertension. Furthermore, a routine color Doppler US, a low-cost and noninvasive procedure, should be considered even in low-risk patients who undergo splenectomy for trauma and who have no underlying hematologic disease.

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Radiofrequency Ablation for Hypersplenism in Patients With Liver Cirrhosis: A Pilot Study

Quanda Liu, M.D., Kuansheng Ma, M.D., Zhenping He, M.D., Jiahong Dong, M.D., Xin Hua, M.D., Xuequan Huang, M.D., Liang Qiao, M.D., Ph.D.

Radiofrequency ablation is a relatively new technique used for local ablation of unresectable tumors. We investigated the feasibility and efficacy of radiofrequency ablation for hypersplenism and its effect on liver function in patients with liver cirrhosis and portal hypertension. Nine consecutive patients with hypersplenism due to cirrhotic portal hypertension underwent radiofrequency ablation in enlarged spleens. The ablation was performed either intraoperatively or percutaneously. Patients are followed up for over 12 months. After treatment, between 20% and 43% of spleen volume was ablated, and spleen volume increased by 4%–10.2%. White blood cell count, platelet count, liver function, and hepatic artery blood flow showed significant improvement after 1-year follow-up. Splenic vein and portal vein blood flow were significantly reduced. Only minor complications including hydrothorax (three of nine patients) and mild abdominal pain (four of nine patients) were observed. No mortality or other morbidity occurred. Radiofrequency ablation is a safe, effective, and minimally invasive approach for the management of splenomegaly and hypersplenism in patients with liver cirrhosis and portal hypertension. Increased hepatic artery blood flow may be responsible for sustained improvement of liver condition. Radiofrequency ablation may be used as a bridging therapy for cirrhotic patients waiting for liver transplantation. (J GASTROINTEST SURG 2005;9:648–657)

KEY WORDS: Radiofrequency ablation, spleen, hypersplenism, portal hypertension, liver cirrhosis

Esophageal variceal bleeding and hypersplenism are the two most common complications of portal hypertension. Gastric devascularization to block communications between azygous-portal veins or various shunts (such as Warren shunt) have been the mainstay of the surgical therapy for esophageal variceal hemorrhage. In recent years, however, less invasive treatment modalities such as endoscopic sclerotherapy and band ligation of esophageal varices have gained more popularity and thus become treatments of choices in some centers.[1–3] However, few minimally invasive surgical options are available for the management of secondary hypersplenism. The classic splenectomy is associated with loss of the splenic immunity and high morbidity and mortality rates. Splenic artery embolization, a procedure initially described by Maddison in 1973,[4] was used for the management of hypersplenism but was later found to be associated with severe complications, such as splenic abscess, fatal pneumonia, sepsis, pancreatic and hepatic infarction, and even death.[5,6] This procedure was then modified to be partial splenic embolization (PSE), which was not a safe procedure either, because complications such as abdominal pain, fever, atelectasis, or even death occurred.[7–9]

Radiofrequency ablation (RFA) is a relatively new technique used for local ablation of tumors not amenable to surgical resection. It has been successfully adapted as a treatment modality of primary and metastatic tumors of the liver, kidney, breast, and bone[10–13] with the advantages of minimal invasion, rapid recovery, shorter hospitalization, and significant clinical outcome.

To explore whether RFA is a feasible and safe treatment modality for secondary splenomegaly, we previously conducted an experimental study in dogs with splenomegaly induced by splenic vein ligation. The study revealed that RFA is a feasible, effective, and safe procedure for experimental splenomegaly.[14]

From the Institute of Hepatobiliary Surgery (Q.L., K.M., Z.H., J.D.), Chinese PLA General Hospital, Beijing, China; Institute of Hepatobiliary Surgery (Q.L., K.M., Z.H., J.D.) and Departments of Ultrasound (X.H.) and Radiology (X.H.), Southwest Hospital, Third Military Medical University, Chongqing, China; and Storr Liver Unit, Westmead Millennium Institute and Department of Gastroenterology and Hepatology, University of Sydney at Westmead Hospital (L.Q.), Westmead, New South Wales, Australia.
Reprint requests: Liang Qiao, M.D., Ph.D., Storr Liver Unit, Westmead Millennium Institute and Department of Gastroenterology and Hepatology, University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia. e-mail: qlia8530@usyd.edu.au

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To further investigate the feasibility, efficacy, and safety of this procedure in the management of human hypersplenism, we recently performed RFA in a series of nine consecutive patients with severe hypersplenism complicating liver cirrhosis. This is, to the best of our knowledge, the first study reported in the literature on the use of RFA in the management of hypersplenism. Our preliminary results showed that RFA is an alternative minimally invasive technique for severe hypersplenism: it can considerably improve hypersplenism, liver function, and portal hypertension without significant complications. We believe that, if coupled with endoscopic therapy for esophageal varices, RFA may be used as a "bridging treatment" for cirrhotic patients awaiting liver transplantation.

MATERIAL AND METHODS

This study was approved by the Institutional Subcommittee for Innovative Technology and Ethics Committee of Southwest Hospital, Third Military Medical University, PR China. Written informed consent for both surgical intervention and RFA was obtained from each patient prior to the commencement of this study.

Patients

Nine consecutive patients with severe hypersplenism, including two men and seven women (age range, 30–52 years; median age, 52 years), were recruited between March and June 2003 for this study. In all cases, hypersplenism was a complication of portal hypertension associated with chronic liver disease. The diagnosis of liver cirrhosis and portal hypertension was established on the basis of typical clinical findings and laboratory evaluations, including liver function test, hepatitis virus serology, and imaging studies (ultrasonography, barium swallow, and computed tomography scan). Liver biopsies were performed in four cases, which confirmed the clinical diagnosis. Severe hypersplenism was defined as splenomegaly, leukopenia (white blood cell count $<3 \times 10^9$/L), and thrombocytopenia (platelet count $<50 \times 10^9$/L). In eight of nine patients, liver cirrhosis resulted from chronic viral hepatitis, as demonstrated by positive hepatitis B surface antigen (HBsAg), positive hepatitis B core antibody (HBcAb), and positive hepatitis B associated e antigen or antibody (HBeAg/Ab). One of these cases (patient 1) was superinfected with hepatitis D virus, as revealed by positive hepatitis D IgM antibody. In one case (patient 4), complicated intrahepatic ductal stones were present and the patient underwent cholangiojejunostomy 2 months prior to the study. Detailed information about patient demographics, diagnosis, Child-Pugh classification, past history of variceal bleeding, RFA routine, and surgical procedures is given in Table 1.

Bone marrow aspiration was performed in each patient via iliac crest 1 week prior to RFA for the assessment of the marrow functional status, including cellularity of the marrow and various cell lines, as well as type of erythropoiesis. Eight patients had hyperplasic marrow, and one (patient 7) had hypoplasic marrow. All patients had poor platelet production.

METHODS

Perioperative Preparation

All patients fasted for 12 hours before commencement of the subsequent procedures. Nasogastric tubes and urethral catheters were placed. Two electrode pads (grounding pads) were placed on lumbar flanks. RFA was performed with the patients under general anesthesia. Prophylactic antibiotics were used intraoperatively and postoperatively.

Radiofrequency Ablation Systems

An LDRF-50CA RFA system (Lead Electron Corp., Mianyang, Sichuan Province, China) with an operational principle similar to that of the RF 2000 generator system (RadioTherapeutics Corp., Mountain View, CA) was used in all patients. This system consists of a generator that supplies up to 90 W of power, a 15-gauge retractable array needle electrode of 15 cm in length, two to four bipolar electrodes, and two electrode pads (grounding pads).

The needle electrode is an insulated cannula containing five individual hook-shaped retractable electrode arms with a maximum expansion of 5-cm array diameter. There are several major differences between the LDRF-50CA system and RF 2000 generator systems. (1) The LDRF-50CA system uses circumvolved bipolar needle electrodes so that an electric circuit could be formed within two electrodes and thus a relatively bigger area can be ablated. (2) An electric circuit also could form within one needle electrode and grounding pad. (3) Changes in the array electrode expansion status, impedance, and power curves are displayed on a computer monitor.

Ablation Procedures and/or Combined Operations

The spleen was accessed percutaneously via the left lateral subcostal approach under sonographic guidance (Fig. 1, *A*) or intraoperatively (Fig. 1, *B*). Two needle electrodes were inserted perpendicularly

Table 1. Patient characteristics, liver function, radiofrequency ablation (RFA) procedures, and combined operations

Patient	Gender	Age (yr)	Etiology	Child-Pugh grade	History of variceal bleeding	RFA pathway†	Occlusion of splenic artery	Simultaneously combined operations	Biopsy of bone marrow	Volume ratio (ablated/whole spleen)	Volume ratio (pre-/post-RFA)
1	F	58	Viral hepatitis B, D	B	−	Laparotomy	Yes	Right-sided cardiac devascularization	Hyperplasia	89.9%	89.2%
2	M	53	Viral hepatitis B	A	−	Laparotomy	Yes*	Right-sided cardiac devascularization	Hyperplasia	43.1%	110.2%
3	M	59	Viral hepatitis B	B	+	Percutaneous	No	Right-sided cardiac devascularization	Hyperplasia	31.8%	106.1%
4	F	52	Intrahepatic stones	B	+	Laparotomy†	No	Distal splenic-caval vein shunt	Hyperplasia	40.2%	105.3%
5	F	30	Viral hepatitis B	B	−	Percutaneous	No	—	Hyperplasia	20.6%	104.0%
6	F	37	Viral hepatitis B	B	+	Percutaneous	No	Right-sided cardiac devascularization	Hyperplasia	34.5%	104.0%
7	F	46	Viral hepatitis B	C	+	Laparotomy‡§	No	Right-sided cardiac devascularization	Hypoplasia	23.3%	107.2%
8	F	52	Viral hepatitis B	B	−	Percutaneous	No	—	Hyperplasia	28.4%	107.1%
9	F	40	Viral hepatitis B	B	−	Laparoscopic	No	—	Hyperplasia	23.5%	105.3%

*Splenic artery reopened after RFA procedure.
†Surgical procedures prior to splenic RFA.
‡Except in patients 4 and 7, the simultaneously combined operations were performed after splenic RFA.
§Because of inconvenient access to splenic vein, the planned distal splenic-caval vein shunt was converted to right-sided devascularization of the gastric cardia.

into splenic parenchyma 3–5 cm in depth away from splenic capsule, hilum, and larger vessels. After deployment, the hook-shaped retractable electrode arms were opened vertically, and RFA energy was applied with an initial power output of 50 W. The LDRF-50CA system works automatically thereafter, with a rise in impedance and an automatic adjustment in power. The power supply is terminated when the impedance reaches maximum. The electrode was rotated in situ and retracted for 2.0 cm, and the above session was repeated. The needle track was cauterized upon the needle withdrawal. Three or four overlapped regions in the mid to inferior part of the spleen were ablated for each treatment session. During the RFA procedure, dynamic ultrasound images of ablated spleen were recorded.

As shown in Table 1, of the nine patients, four had RFA during the open surgery (laparotomy), and one had RFA laparoscopically. Five patients had simultaneous right-sided pericardiac devascularization to stop the azygoportal communication. Four patients underwent RFA percutaneously, of whom two received splenic RFA percutaneously only, and in the other two patients, percutaneous RFA was performed along with right-sided cardiac devascularization. One patient (patient 4) also underwent distal splenic–caval vein shunt, a procedure similar to distal splenic–renal vein shunt (Warren shunt).

Patient Follow-up

All patients were closely followed for over 12 months. For evaluation of acute and chronic complications after RFA, serum and urine amylase levels were checked in all patients immediately after RFA and repeated in 7 days. The following tests were performed while the patients were in the hospital and repeated in 3 weeks, 2 months, 6 months, and 1 year after RFA: hemoglobin, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), Child-Pugh score, and abdominal ultrasound. Abdominal CT scans were performed 7–10 days, 2 month, and 1 year after RFA. All of the clinical symptoms were recorded in detail.

In addition, the whole spleen volumes and the volumes of the ablated zones within the spleen were measured 1 week before and 7–10 days after RFA, and the volumetric changes of the spleen as well as the ratio of the ablated areas relative to whole spleen were calculated. The margin of the RF-ablated lesion was defined by a high-density rim that can be visually detected. Only the nonenhanced area within the spleen was considered a thermally induced lesion. The whole spleen volume and the size of ablated lesions were calculated using automated

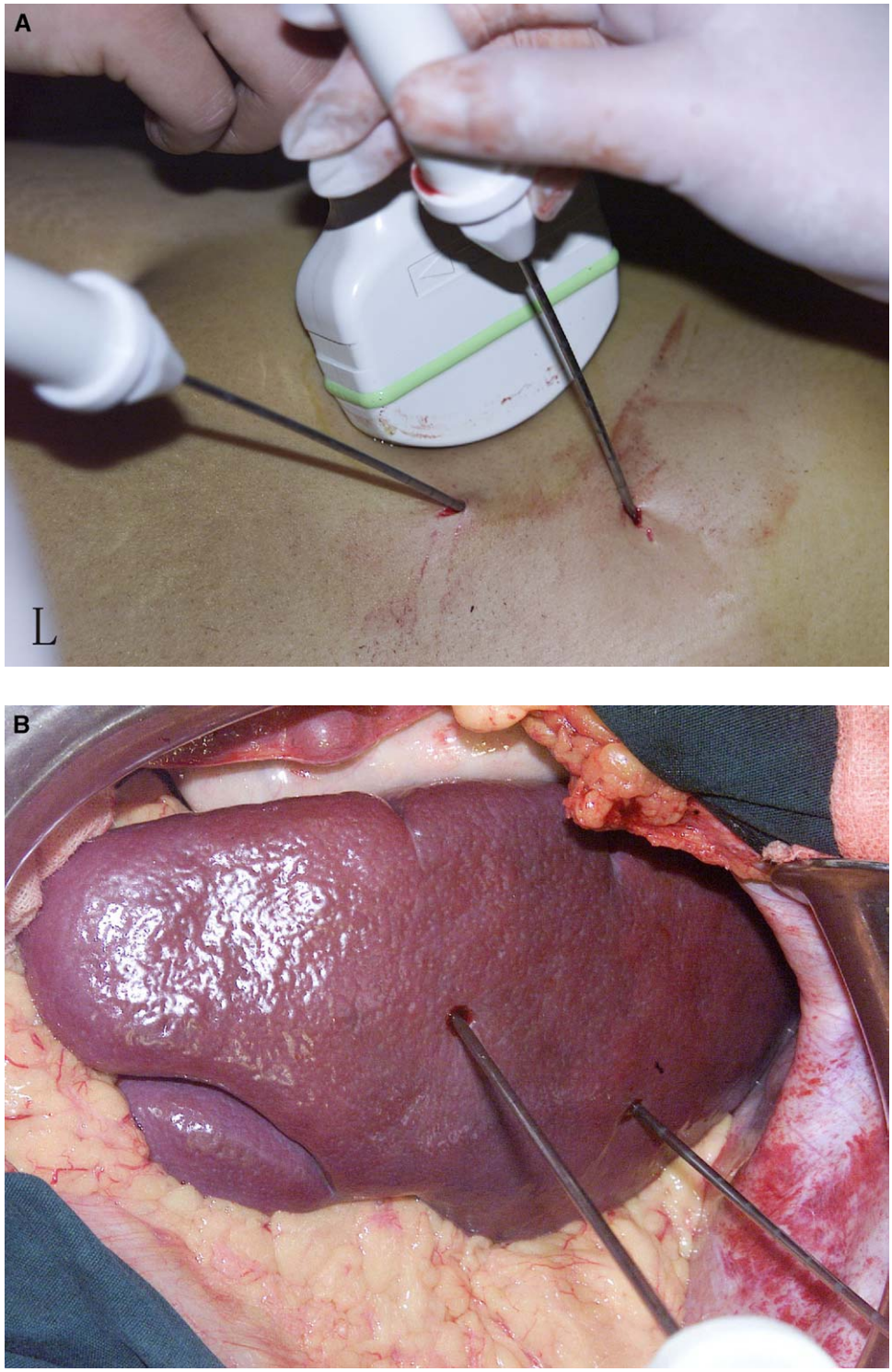

Fig. 1. The spleen was accessed percutaneously via the left lateral subcostal approach under sonographic guidance (**A**) or intraoperatively (**B**).

segmentation algorithms (Volume Calculating Software, SOMATOM Plus 4; Siemens Medical System, Erlangen, Germany).

Apart from real-time gray-scale imaging, the blood flows of portal vein, hepatic artery, and splenic vein were also determined by duplex Doppler velocity and color Doppler flow mode using a 3.5-MHz convex, linear-array probe (SSD-1700; Aloka, Tokyo, Japan).[15,16]

The clinical efficacy of the RFA was assessed by leukocyte and platelet counts in peripheral blood

samples after the procedure. The therapeutic response was evaluated immediately after the procedure and throughout the follow-up period. Serum creatinine, urea, and glucose concentrations were also measured during follow-up.

Statistical Analysis

All data are expressed as mean ± SD. A paired *t* test was used to evaluate the laboratory changes and CDFI indices before and after splenic RFA. A value of $P < 0.05$ was considered statistically significant. All statistics were analyzed using SPSS version 10.0 software.

RESULTS

Image Study of the Spleen After RFA

Intraoperative ultrasonographic scanning showed that hyperechoic bubble-like changes emerged in the area around RF electrode needle (indicated by hyperechoic signal, Fig. 2, *A*, *a*) and within bipolar electrodes soon after applying splenic RFA (Fig. 2, *A*, *b*), and the hyperechoic area gradually enlarged and diffused. With the increase of impedance, these areas ultimately transform into uniformly diffused hyperechoic plaque-like lesions (indicating the ablated areas) (Fig. 2, *A*). Postoperative ultrasonography demonstrated the coagulative necrotic area as irregular hyperechoic lesions with clear contour, surrounded by hypoechoic nonhomogeneous alterations, indicating thrombotic areas (Fig. 2, *B*).

On postoperative CT scan, the ablated lesion comprised of hyperdensity necrotic area and hypodensity infarcted area, with the hypodensity areas generally larger than hyperdensity necrotic areas (Fig. 3). No splenic liquifaction or intrasplenic/perisplenic abscesses were observed. The ablated areas display a fan-like shape, in conformity with the blood vessel distribution of the spleen. The maximum diameter of ablated area was above 10 cm, and that of the coagulative necrosis reached 8 cm in some cases.

The volume ratio of ablated lesions to whole spleen in those without splenic artery occlusion ranged from 20% to 43% (mean, 30.7%). In patient 1, in whom permanent occlusion of splenic artery was performed, RFA destroyed 89.9% of the spleen volume. In other patients, the average whole spleen volume 7–10 days after RFA slightly increased from 104.0% to 110.2% of the pre-RFA volume (1323.5 ± 280.2 cm^3 and 1281.6 ± 317.5 cm^3, respectively), but this was not statistically significant ($P = 0.77$). Refer to Table 2 for details.

In addition, significant liver regeneration was noted on CT scans in some patients.

Blood Flow Indices

No hepatofugal flows were detected in all cases. The average values of portal vein flow (PVF), splenic vein flow (SVF), and hepatic arterial flow (HAF)

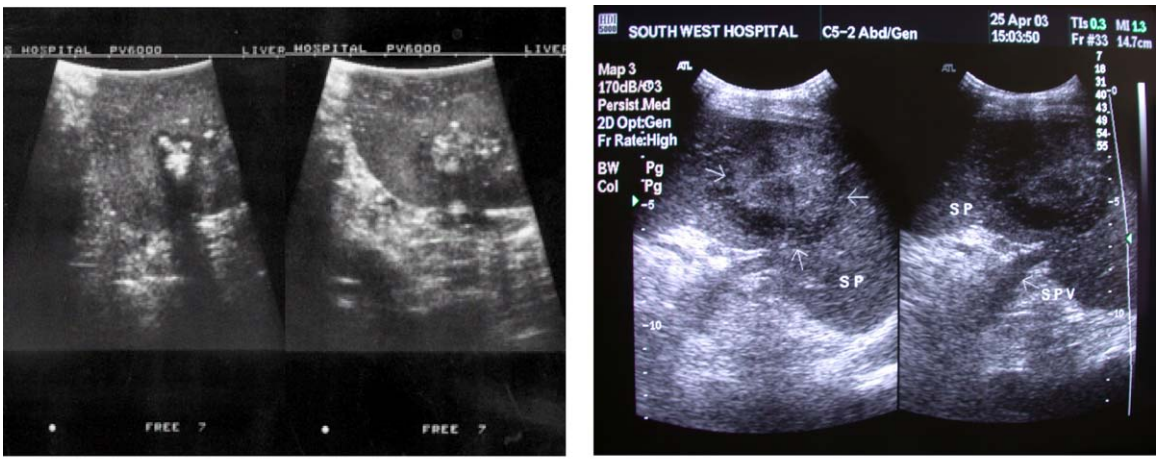

Fig. 2. (**A**) Intraoperative ultrasonographic scanning showing hyperechoic bubble-like changes in the area around the radiofrequency electrode needle as indicated by hyperechoic signal (**a**) and within the bipolar electrodes (**b**). (**B**) Postoperative ultrasonography showing the coagulative necrotic area as irregular hyperechoic lesions with a clear contour (**a**), and these lesions are surrounded by hypoechoic nonhomogeneous alterations (**b**).

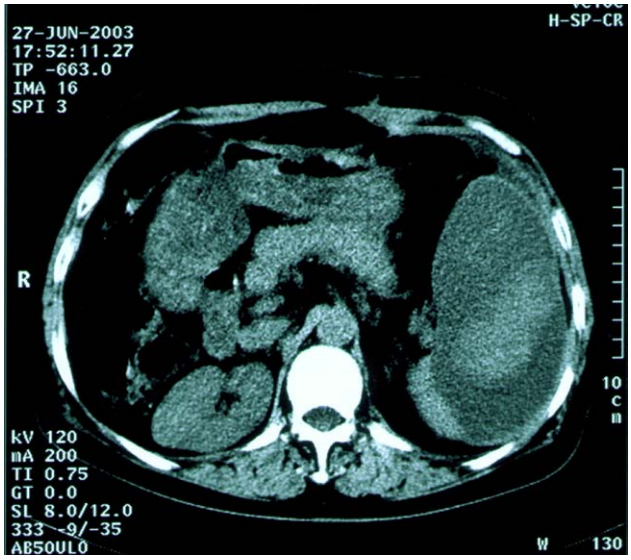

Fig. 3. Postoperative computed tomography scan.

before and after RFA are shown in Figure 4. The SVF was markedly reduced after splenic RFA ($P < 0.0001$), and so was the PVF ($P < 0.001$). On the contrary, the HAF was significantly increased as compared to baseline values ($P < 0.001$). The percentage of hepatic arterial flow to total liver blood flow was 9.9% before splenic RFA and 34.7%, 35.8%, and 26.9% at 1 month, 2 months, and 1 year after RFA treatment, respectively.

Laboratory Examinations

Peripheral blood examination revealed a rapid increase in leukocytes and platelets after RFA treatment. The results of the average measurement of white blood cells (WBCs) and platelets (PLTs) showing their trends following RFA are shown in Figure 5, *A*. As can be seen, the average WBC count increased significantly soon after RFA with a peak appearing within 1–3 days after RFA. Thereafter, except in case 7, the WBC counts remained above 4.0×10^9/L. Even 60 days after the procedure, WBC count was still significantly higher than the pre-RFA baseline ($5.1 \pm 0.8 \times 10^9$/L versus $2.1 \pm 0.4 \times 10^9$/L, respectively, $P < 0.001$). The average PLT count significantly increased 5 days after RFA ($79 \pm 46 \times 10^9$/L versus pre-RFA counts of $28 \pm 10 \times 10^9$/L, $P < 0.01$), and normal counts were observed 10 days after RFA ($130 \pm 77 \times 10^9$/L), with a peak appearing 14 days after RFA ($159 \pm 107 \times 10^9$/L, $P < 0.01$, compared with pre-RFA baseline counts). The PLT count remained at higher than baseline levels 1 year after RFA ($89 \pm 32 \times 10^9$/L). Thus, leukopenia and thrombocytopenia of these patients were significantly improved. However, in patient 7, whose bone marrow was previously hypoplasic, a status of cytopenia reappeared 2 months after RFA (WBC count: 3.8×10^9/L; PLT count: 53×10^9/L).

Table 2. Measurement of splenic volume changes 7 days before and after radiofrequency ablation (RFA) in patients with liver cirrhosis and portal hypertension

Measurement	Pre-RFA	Post-RFA
Splenic volume (cm^3)	1281.6 ± 317.5	1323.5 ± 280.2
Ablated area (cm^3)		497.2 ± 346.9
Ratio of ablated area to post-RFA splenic volume	—	37.2 ± 0.2%
Splenic volume change (relative to pre-RFA size)	—	104.3 ± 0.06%

In patient 1, the post-RFA splenic volume was slightly decreased to 89.2% of the pre-RFA size, and 89.9% of the splenic volume was ablated. All other patients had their spleen size enlarged after RFA. Data are expressed as mean ± SD (n = 9).

The results of liver function tests are shown in Figure 5, *B*. It can be seen that the prothrombin time (PT) was restored to normal at the seventh post-RFA day from a pre-RFA value of 17.3 ± 2.7 seconds to the post-RFA value of 14.7 ± 1.7 seconds ($P < 0.05$). Both ALT and AST increased transiently 3 days after splenic RFA treatment but returned to normal on the fifth post-RFA day. All liver function tests still remained within normal range 1 year after RFA.

The serum and urine amylase levels 7 days post-RFA were within normal limit. No hemoglobin changes were noted post-RFA (data not shown).

Complications

No obvious bleeding occurred after the insertion of the RF electrodes into the spleen, regardless of whether the splenic artery is occluded. Minor bleeding around the electrodes stopped spontaneously several minutes after initiating RFA. No thermal injuries of perisplenic organs, such as pancreas, stomach, and colon, were detected. No fluctuation in blood pressure was observed and all patients began oral feeding 3 days post-RFA with uneventful recovery. No hyperpyrexia (>38°C), gastrointestinal perforation, peritonitis, intra-abdominal hemorrhage, and rupture of spleen occurred. Asymptomatic hydrothorax occurred in three patients; only one required one-time pleural effusion drainage. All hydrothorax disappeared 1 month after splenic RFA, as confirmed by ultrasound. Four patients had mild abdominal pain around the splenic area, of whom three had their pain settled within 7 days after RFA, and one had the pain settled on the 11th day after RFA; thereafter, no

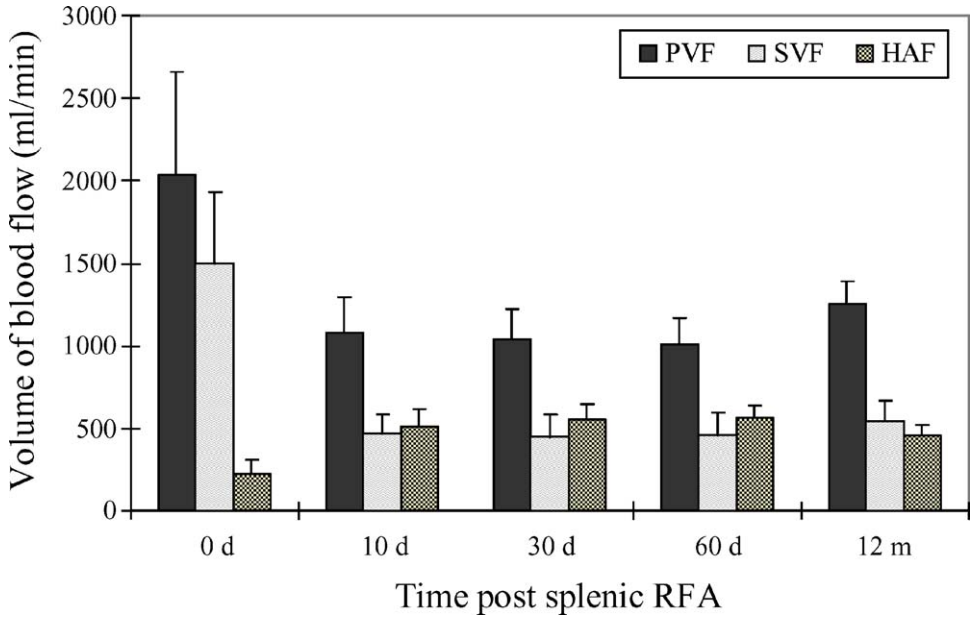

Fig. 4. Volume of blood flow versus time after splenic radiofrquency ablation.

recurrent abdominal pain occurred. No patients required additional pain control. No esophageal variceal bleeding occurred in all patients during the follow-up period, as determined by esophagogastroendoscopy and barium meal.

DISCUSSION

Splenectomy coupled with cardiac devascularization and transcatheter selective splenic arterial embolization has been frequently used for treatment of hypersplenism in patients with portal hypertension.[17,18] In most patients, these procedures are effective in preventing esophageal variceal hemorrhage and in correcting thrombocytopenia and leukopenia (hypersplenism). However, these procedures are associated with certain complications and high morbidity and mortality rates. Safer and less invasive surgical approaches in the management of patients with hypersplenism and portal hypertension are still far from development.

RFA has been widely used to treat tumors of solid organs.[10–13] Recent advancement of RF equipment has extended its utility to such splenic conditions as metastases of colonic and renal malignancies,[19,20] hypersplenism, splenic injury, and partial splenectomy.[21] Previous animal experiments by our group have confirmed that RFA is a safe and feasible treatment for splenomegaly in a canine model.[14]

In our current study, RFA was used to treat cirrhotic hypersplenism, a very common condition in China often associated with low immunity and high chance of fatal bleeding from varices. Because we thought fatal bleeding might occur in these patients in whom coagulopathy was present, we took extra caution in patient 1 by ligating the splenic artery before RFA. In patient 2, the splenic artery was clamped during the RFA and reopened after the procedure was completed. Through these two patients, we were able to demonstrate that RFA was safe in patients with hypersplenism; therefore, we did not perform splenic artery occlusion in the other seven patients before RFA. After RFA, no massive intra-abdominal hemorrhage and thermal injuries to the surrounding organs such as pancreas, stomach, and intestines were noted. Thus, we believe that splenic RFA (either percutaneously or via laparotomy) for cirrhotic patients with hypersplenism was a safe procedure.

No mortality occurred in our patients after RFA in enlarged spleen, nor did we see any major complications such as hyperpyrexia, splenic abscess, and splenic rupture, which are complications that frequently occur after partial splenic embolization. However, three of nine patients (33.3%) had mild to moderate pleural effusion, which we believe could have been prevented if the electrodes had been inserted at middle and inferior parts of spleen to avoid the upper part of spleen being ablated. Mild abdominal pain occurred in four of nine (44.4%) patients, possibly attributable to a smaller RFA lesion and less swelling of spleen volume (spleen swells to 104.3% of the pre-RFA size in our series, compared with the reported 110%–140% in PSE patients[22]).

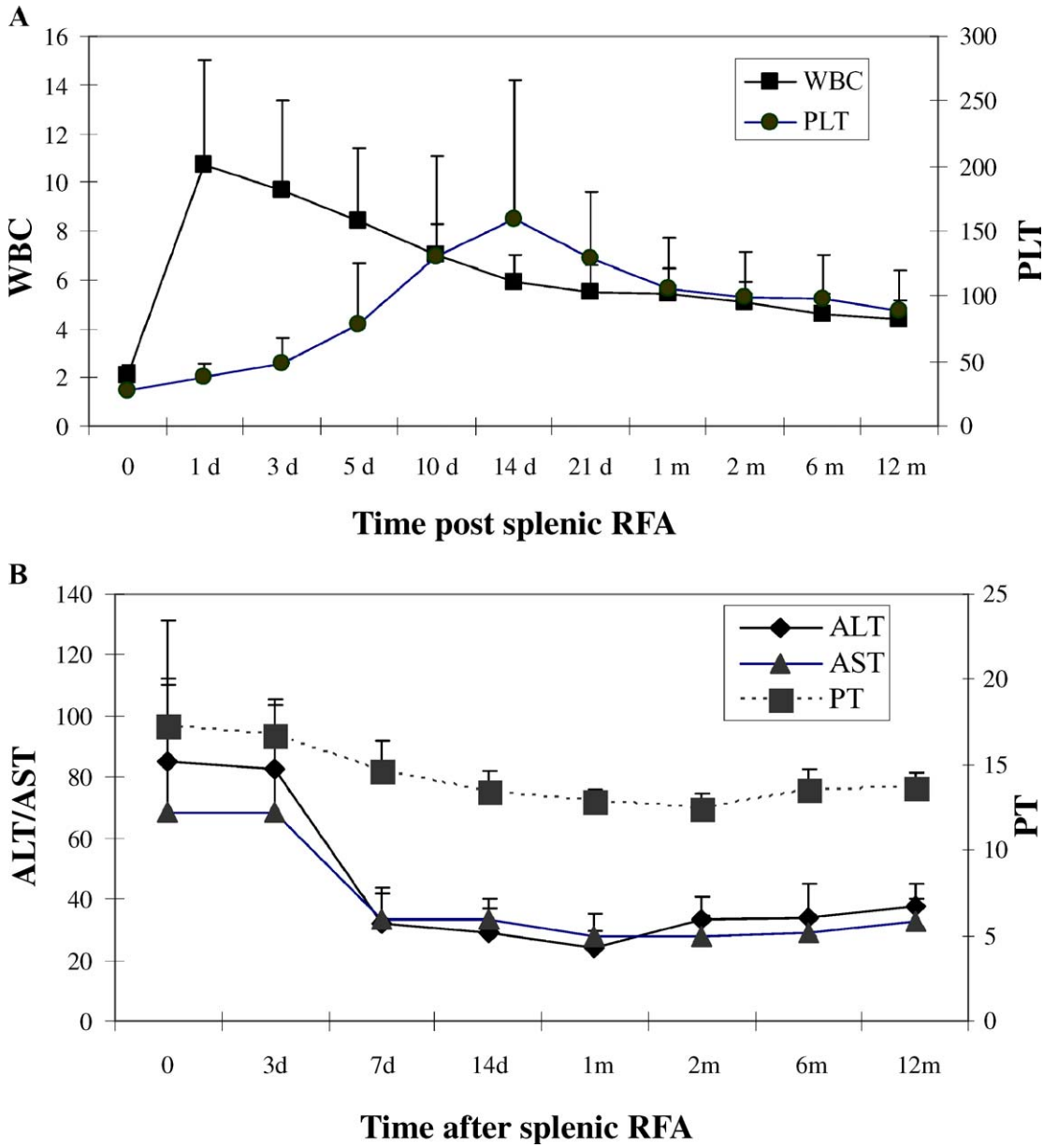

Fig. 5. Measures of white blood cells (WBC) and platelets (PLT) (**A**) and alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT) (**B**) versus time after splenic radiofrequency ablation.

The minor bleeding around the electrode path terminated spontaneously soon after initiating RFA, as RF energy can cauterize the blood vessel to cause electric coagulation. Blood vessels less than 3 mm in diameter in ablated areas soon thrombosed after RFA was initiated; thus, no major bleeding occurred.

Because the spleen is a highly vascularized organ, it is conceivable that RFA of the spleen may potentially cause thermal injury to surrounding tissues/organs such as liver, pancreas, and intestines, as RFA heat may be carried away from the target lesion through splenic vein. Previous study by others also recommended that occlusion of splenic hilum may be necessary before RFA is initiated, and the "heat-sink" phenomenon of the spleen may limit tissue heating and thus affect the tissue ablation.[19] We noticed thermal injury in our animal experiments.[14] However, in our current human study, no obvious "heat-sink" and thermal injuries to surrounding tissues and organs occurred. This could be explained by chronic fibrosis of splenic parenchyma and enlarged spleen size, which confines the RF heat exchange within spleen.

One-year follow-up of these patients revealed that after splenic RFA, the majority of the patients had significant improvement in hypersplenism/peripheral blood counts. Only one patient (patient 7) did not have noticeable improvement in hypersplenism, possibly because of the previous hypoplasic bone marrow.

Interestingly, we found that there was a dramatic improvement in liver function tests. Three major indices of liver function tests, ALT, AST, and PT, were significantly improved. This improvement may be attributable to the combination of a reduced blood flow of the splenic and portal vein (by as much as 70% and 50%, respectively) and stably increased flow of hepatic artery. It has been known that the dual blood supply to liver is regulated by hepatic arterial buffer response: a reduction of blood flow in the portal vein triggers an increase in blood flow of the hepatic artery. Studies have demonstrated that following RFA, hepatic artery blood flow can increase by 2.1- to 2.5-fold. Increased hepatic arterial blood flow can in turn increase the oxygen supply to the liver and improve the capacity of hepatic oxygen exchange[23]; thus, liver function can be ameliorated (oxygen limitation theory).[24,25] These studies also showed that the low hepatic arterial flow in the cirrhotic human liver was significantly increased by graded regional infusion of adenosine into branches of the hepatic artery. This increase in hepatic blood flow lead to a greatly improved metabolic capacity of hepatocytes to oxidative drugs. On the other hand, reduction in portal vein pressure may also lead to improvement of congestion of liver sinusoids. All these changes may be responsible for the improvement of liver function tests. Further studies with a larger sample size and longer follow-up will be needed to evaluate how long the improvement in the liver function lasts.

Improved liver function may contribute to improved PLT production after RFA, as thrombopoietin, a factor that stimulates PLT production by megakaryocytes, is almost exclusively synthesized by liver.[26]

In comparing with PSE on hypersplenism,[27] both procedures have similar therapeutic principles. However, RFA has significant advantages, such as more confined lesion, less frequent and milder complications, convenient performance, and cheaper equipment requirements. Further studies are warranted to determine how best therapeutic benefit can be obtained with minimum ablation of spleen tissue in the management of hypersplenism.

In summary, this study demonstrated that RFA is a promising therapeutic approach for hypersplenism in patients with cirrhosis and portal hypertension. For portal hypertensive patients with liver cancer, both tumor and enlarged spleen may be ablated simultaneously or sequentially. However, extrapolation of the study results is hampered by the limited sample size and relatively short follow-up. More studies with a larger sample size and longer follow-up are needed to further confirm the efficacy of RFA in hypersplenism and to answer such questions as how long the improvement in hypersplenism and liver function lasts, what is the minimally required ablation tissue size for the best therapeutic benefit, and how to combine RFA with other therapeutic approaches to achieve best results. Prospective randomized control trials may also be useful to compare the efficacy of RFA with other therapeutic approaches for portal hypertension.

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Intermittent Hepatic Vein–Total Vascular Exclusion During Liver Resection: Anatomic and Clinical Studies

Shawn MacKenzie, M.D., Elijah Dixon, M.D., Oliver Bathe, M.D., Francis Sutherland, M.D.

Bleeding from hepatic veins remains a problem during liver surgery. Perceived difficulties in the dissection and isolation of these retrohepatic venous structures have limited the widespread use of hepatic vein control during liver resection. The purpose of this study was to delineate the anatomy of the hepatic veins and to apply this knowledge to a series of patients undergoing liver resection with intermittent hepatic vein–total vascular exclusion (IHV-TVE). A detailed description of the hepatic venous anatomy was formulated using 20 cadaveric dissections in conjunction with anatomic descriptions during 30 hepatectomies. With the benefit of improved anatomic knowledge, we evaluated a series of 45 consecutive major liver resections in which hepatic veins were isolated and the technique of IHV-TVE was applied. The hepatocaval ligament must be divided to isolate the right hepatic vein. It was closely associated with a caudate vein 69% of the time. The hepatic veins were isolated in 45 consecutive patients who underwent a major hepatic resection. The portal triad and the hepatic veins were occluded intermittently (20 minutes with 5 minutes of reperfusion) with Rommel tourniquets. Mean total warm ischemic time was 65 ± 24.5 minutes. Mean estimated blood loss was 864 ± 514 ml. Eighteen percent of patients required blood transfusions. Complications were identified in 16 patients (35.5%), and the average length of hospital stay was 10.5 ± 3.4 days. There were no deaths. Detailed anatomic knowledge of the hepatocaval ligament and the hepatic veins allows for safe extrahepatic control of the hepatic veins during major hepatic surgery. The technique was well tolerated and may have limited intraoperative blood loss. (J GASTROINTEST SURG 2005;9:658–666)

KEY WORDS: Liver resection, vascular exclusion, hepatic veins

In 1952, Lortat-Jacob and Robert[1] described the anatomy of the right hepatic vein and the associated hepatocaval ligament, during the first right hepatectomy. Outside the liver, the hepatic veins have a short course and are situated in a strategically difficult location. Injury may result in catastrophic bleeding. In view of this potential risk and perhaps because of an incomplete understanding of the anatomy, the majority of surgeons do not dissect the hepatic veins to obtain vascular control before parenchymal dissection.[2] However, despite technological advances in parenchymal dissection, perioperative hemorrhage from these veins within the liver remains the principal concern during major hepatic resections. Damage to venous tributaries and subsequent bleeding can occur throughout the parenchymal dissection, obscuring the operative field and risking air embolus. Significant bleeding may also make identification of the dissection planes difficult, compromising resection margins. A more detailed understanding of the hepatic veins and the ligamentous attachments surrounding the upper inferior vena cava (IVC) may improve the safety of isolation of these veins in their extrahepatic location.

To enhance our capability to control the hepatic veins, we formally studied the anatomy of the hepatic veins and the hepatocaval ligament. Our observations were applied in a clinical series, where the hepatic veins were routinely isolated in consecutive patients undergoing major hepatic resection under intermittent hepatic vein–total vascular exclusion (IHV-TVE).

From the Department of Surgery, Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada.
Reprint requests: Dr. Francis Sutherland, Tom Baker Cancer Centre, 1331 29th Street N.W., Calgary, Alberta, Canada T2N 4N2. e-mail: Francis.Sutherland@CalgaryHealthRegion.ca

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METHODS

Anatomic Studies

Hepatocaval ligament and hepatic vein anatomy were studied in two contexts: first, in 20 fresh cadaveric dissections, and then the anatomy was recorded during our most recent 30 hepatectomies. All anatomic data were obtained from adults. In the cadaveric studies, the liver was approached, as in a live dissection, using a bilateral subcostal incision. The right liver was mobilized and the hepatocaval ligament was dissected without division. Silicone casts of Reprosil dental casting material (Dentsply International, York, PA) were made of the IVC and hepatic veins in 10 of the 20 cadaveric specimens. To perform the casting, the IVC was ligated above the renal veins and the right atrium was accessed through a right thoracotomy incision. Impression material was injected into the hepatic veins and vena cava via the right atrium, after evacuation of blood. We were able to perform multiple casts on each cadaver. Casts were performed in one of three anatomic situations: (1) "in situ," with no liver mobilization (10 cases); (2) with the right hepatic lobe mobilized (5 cases); and (3) with the right lobe mobilized and the hepatocaval ligament cut (4 cases). After the casts were manually extracted through the right atrium, the right hepatic vein and the middle/left common trunk were dissected and encircled. Detailed drawings of the hepatocaval ligament and the hepatic veins were made. During the last 30 hepatectomies, this anatomy was also recorded. All surgical dissections were performed in a standardized fashion, allowing comparison with cadaveric casts. Histologic studies of the hepatocaval ligament were done with routine hematoxylin and eosin staining and microscopic examination.

Operative Approaches to Hepatic Vein Isolation

Encirclement of the right hepatic vein required mobilization of the right lobe and division of the hepatocaval ligament. Vascular clips were placed across the ligament to control bleeding from small veins located posterior or within the main ligament. To safely isolate the inferior aspect of the right hepatic vein, the IVC was separated from the caudate lobe by clipping small caudate veins and/or suture ligating substantial veins. A deep space was developed parallel to the IVC, between the right vein and common trunk of the middle and left hepatic veins. A right-angled clamp was used to connect these superior and inferior dissections, allowing vascular occlusion with umbilical tape supported with a Rommel tourniquet (Fig. 1). Large inferior right hepatic veins were also controlled with Rommel tourniquets.

The middle and left hepatic veins were isolated around their common trunk. Segments 2 and 3 were reflected to expose the ligamentum venosum and the top of the caudate lobe. The left hepatic vein was reflected superiorly with segment 2. The peritoneum and loose connective tissue between the middle hepatic vein and upper portion of the caudate lobe were separated, and a space between the middle hepatic vein and the IVC was developed. From the opposite side, a space was developed between the middle and right hepatic veins, allowing dissection under the middle hepatic vein. The lateral and medial dissections were connected; an umbilical tape was passed under the middle hepatic vein, encompassing the entire common trunk (Fig. 2).

A large central caudate vein lies approximately 2–3 cm directly caudal to the middle hepatic vein. This vein was deliberately identified by dividing the hepatocaval ligament on the left side and reflecting the lateral caudate lobe off the IVC.

Clinical Series

Forty-five consecutive patients who underwent a major liver resection (i.e., at least two segments) were accrued prospectively, between 1999 and 2003. Patients undergoing wedge resections and patients undergoing resections for gallbladder cancer (segments 4 and 5) were excluded, as the hepatic veins were not isolated in these anterior resections. Outcome measures included mortality, perioperative blood loss, transfusion rate, complication rate, operative duration, and length of hospital stay. Hilar dissection was not routinely performed. Rather, the Glissonian sheaths were taken within the parenchyma with vascular staplers, during vascular exclusion. The hepatic veins were also stapled within the parenchyma while they were being controlled in the extrahepatic location with a Rommel tourniquet. Hepatic exclusion was achieved with an intermittent technique: the portal triad and hepatic vein(s) were occluded with Rommel tourniquets for 20 minutes followed by 5 minutes of reperfusion. During reperfusion, the liver was compressed to prevent bleeding. The technique of liver parenchymal dissection changed over the study period. In the first 12 (27%) patients, a hemostat ("crush" technique) was used. In the next 22 (49%) patients, parenchymal transection was performed with the CUSA (Valley Labs, Boulder, CO), and the last 11 (24%) patients were treated with the harmonic scalpel (Ethicon Canada, Toronto, Ontario, Canada). All liver resections included a cholecystectomy. No strict policy on central venous pressure (CVP) was used. However, in the past 2 years, efforts to maintain a CVP of less than 5 cm H_2O 3 were initiated.[3]

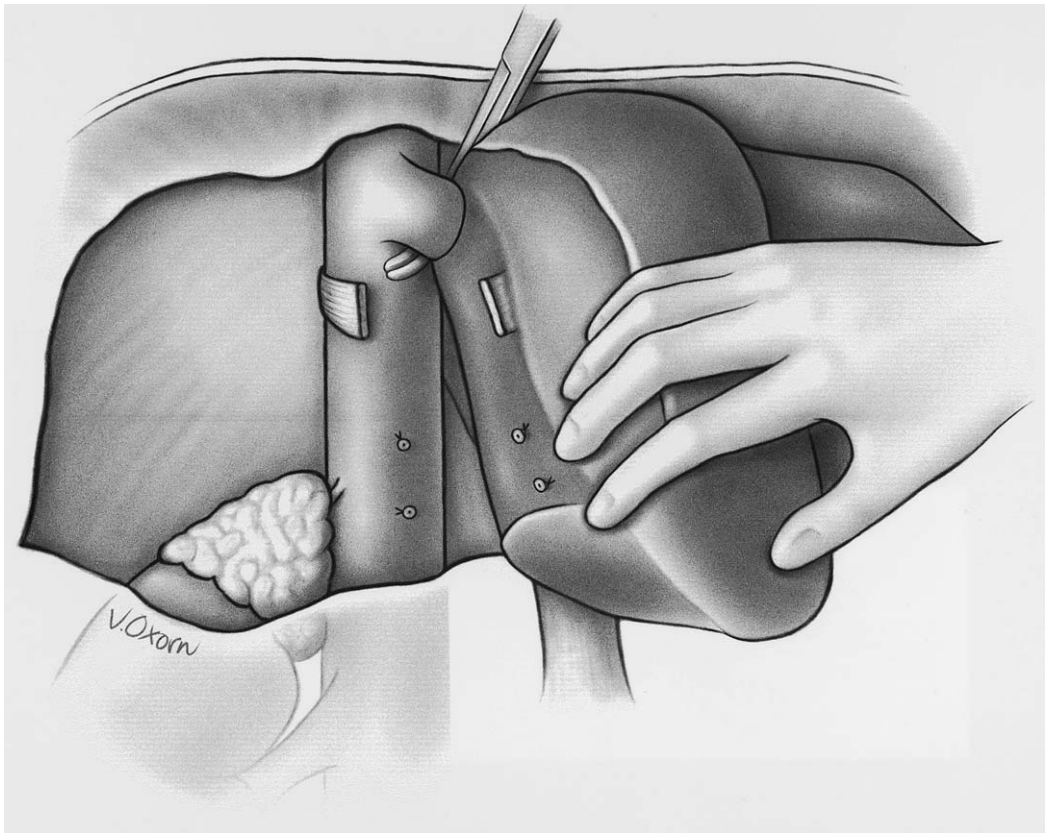

Fig. 1. Encircling the right hepatic vein with right angle, after division of the hepatocaval ligament.

Fibrin glue (Tisseel; Baxter Corp, Mississauga, MS) was used routinely on the cut parenchymal surface before closure. The decision to transfuse packed red blood cells was at the discretion of the surgeon and the anesthesiologist, based on clinical evaluation of the patient.

Estimated blood loss (EBL) was determined by the surgeon's perception of perioperative blood loss (in consultation with the anesthesiologist). Complications were recorded prospectively and graded according to the scale developed by Martin et al.[4] Perioperative blood transfusion was defined as a transfusion received during the initial hospitalization or anytime in the first 30 days postoperatively.

Statistical Analysis

All data are expressed as mean ± SD, and range, unless otherwise indicated. Univariate comparisons were tested using the Fisher exact test or χ^2 test for dichotomous covariates. Continuous variables were compared using *t* tests. Differences were considered significant at $P < 0.05$. Multivariate analysis was performed to assess the impact of covariates on complication rate and transfusion rate. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC).

RESULTS

Hepatocaval Ligament Anatomy

The hepatocaval (dorsal IVC) ligament was found in all specimens in various forms. Gross review determined the ligament to be of three types, based on its composition: type 1, entirely ligamentous connective tissue (64%); type 2, a central portion of ligamentous tissue with liver tissue at either end (24%); and type 3, liver tissue in its entirety (12%) (Fig. 3). Microscopic examination of the ligament demonstrated fibroconnective tissue and bile ducts (Fig. 4). In general, the ligament extended from the lateral aspect of segment 7, wrapping posteriorly around the IVC to the caudate lobe (Fig. 5). The ligament originated on the right, as a wide band of fibers (mean, 17.5 ± 7.2 mm; range, 7–40 mm) covering the posterior aspect of the IVC. As it coursed to the left, it narrowed with some fibers splaying out on the IVC (mean, 6.9 ± 4.3 mm; range, 3–20 mm). The ligament thickness varied from a thin film to 2 mm over its course. A small caudate vein was

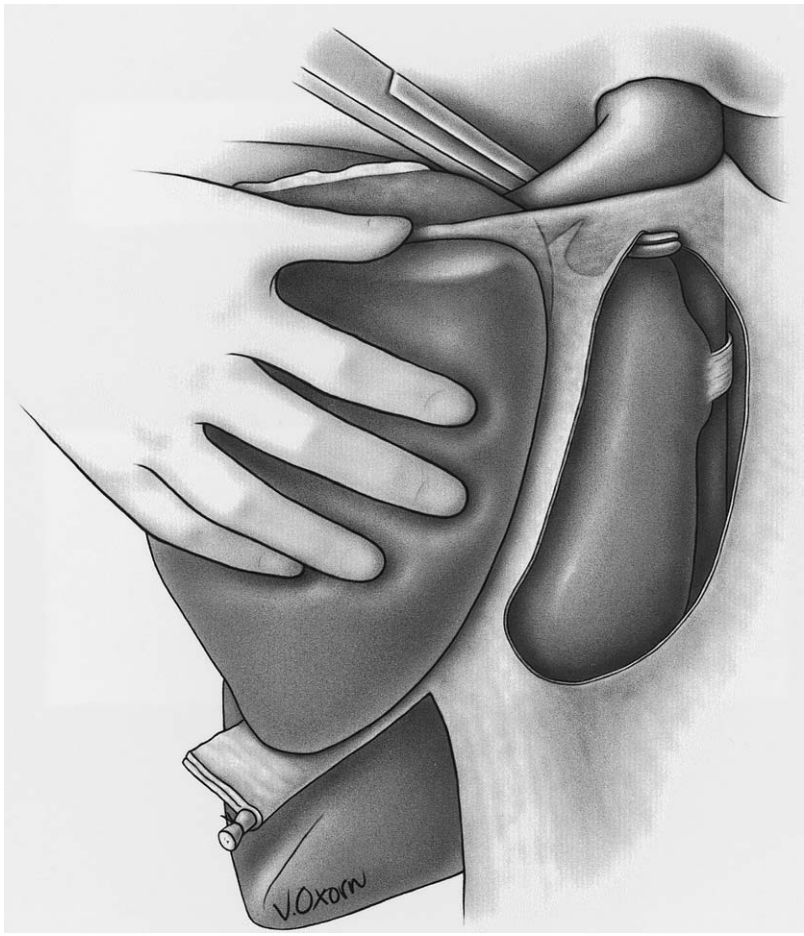

Fig. 2. Encircling the common trunk of the middle/left hepatic vein. The left hepatic vein and ligament venosum (not shown) were mobilized with traction on segments 2 and 3. The right angle passes between the middle hepatic vein and the inferior vena cava, emerging just above the superior portion of the caudate lobe.

identified posterior or within the ligament on the right side in 69% of cases (mean vein size, 2.4 ± 1.1 mm; range, 1–5 mm). Identification of this vein before division of the ligament was difficult.

Venous Anatomy

A common trunk for the middle and left hepatic veins was found in 9 of 10 casts and 29 of 30 liver resections (95%). The right vein orifice was oriented vertically, while the middle/left common trunk was oriented transversely. As a result, the junction of the right hepatic vein and the IVC was caudal compared with the middle/left common trunk. The left hepatic vein extended over the left edge of the IVC and the middle hepatic vein extended inferiorly above the IVC. In all 10-cast specimens, a large central caudate vein was found within 3 cm (range, 1.5–3.0 cm) caudal to the middle hepatic vein. The dissection line around the inferior aspect of the middle hepatic vein was short (i.e., <1 cm) and avascular. Cadaveric dissections and casting studies revealed mobilization of the right liver flattened the right hepatic vein and "kinked" the IVC, reducing the cross-sectional volume. Division of the hepatocaval ligament did not appreciably alter the kinking. Rather, the kinking appeared to be a result of torsion from the fixed attachment of the right hepatic vein on the vena cava. No hepatic vein tributaries were identified in an extrahepatic location, within 0.5–1.0 cm from the IVC.

Clinical Series

In 45 major hepatic resections, the detailed anatomic data obtained in cadaveric studies were used to facilitate hepatic vein isolation. In 22 patients (48.9%), both the right hepatic vein and the middle/left common trunk were isolated, enabling total vascular exclusion (TVE) while preserving caval flow. The right hepatic vein alone was isolated in 6 patients

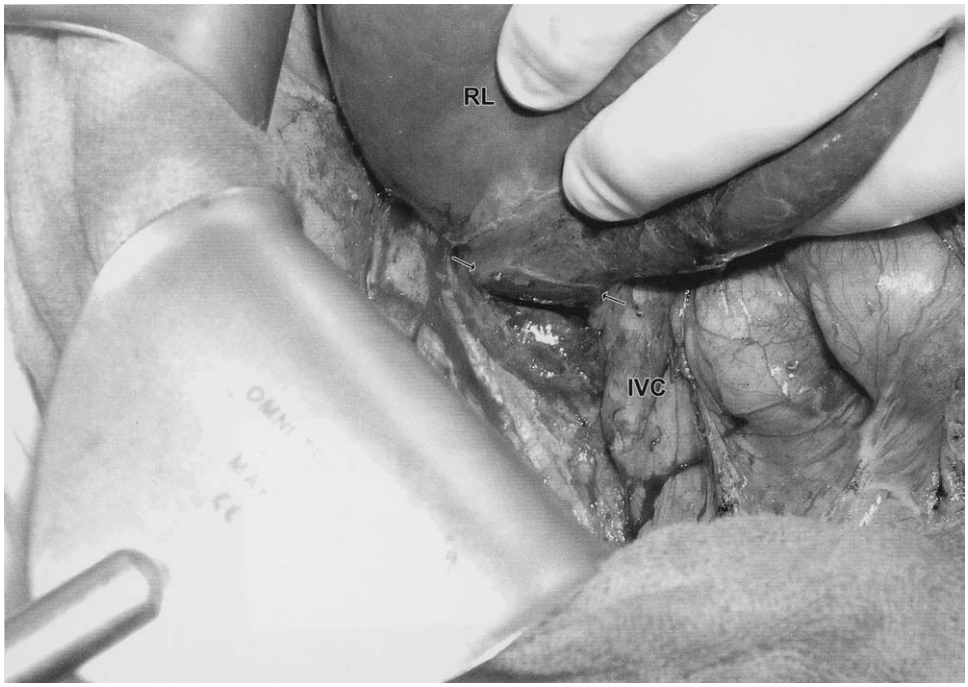

Fig. 3. Type 3 hepatocaval ligament as seen during mobilization of the right lobe of the liver (RL). *Arrows* indicate the hepatocaval ligament, composed of liver tissue, going around the upper inferior vena cava (IVC).

(13.3%), and the middle/left common trunk was selectively encircled in 17 patients (37.8%), for left lateral tumors. We failed to encircle the right hepatic vein in 3 of 31 patients where it was attempted (reoperative surgery, obese patient, type 3 hepatocaval ligament); we had no failures to encircle the middle/left hepatic vein trunk (39 patients). No major bleeding occurred with encirclement of the hepatic veins. Hepatic resections performed included 21 right hepatectomies (46.7%), 2 right hepatectomies extended to segments 4 (4.4%), 8 left hepatectomies (17.8%), 2 left hepatectomies extended to segment 5/8 (6.7%), 3 segment 2/3 resections (6.7%), and 9 other bisegmentectomies (20%).

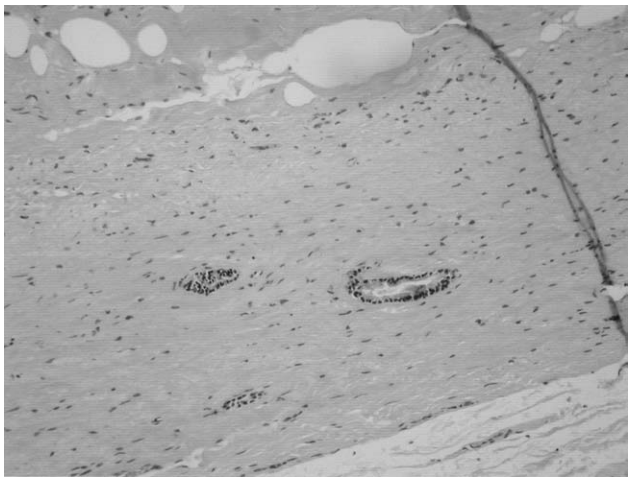

Fig. 4. Photomicrograph of the ligamentous portion of a hepatocaval ligament. The ligament is composed of fibrous connective tissue. Small bile ducts are seen within the ligament.

Patients were predominantly male (66.7%), with an average age of 58 ± 13 years. Four patients (8.9%) had cirrhotic livers. The liver lesions resected were colorectal metastases (24 patients, 53.3%), hilar cholangiocarcinomas (5 patients, 11.1%), hepatocellular carcinomas (5 patients, 11.1%), biliary cystadenomas (5 patients, 11.1%), and other lesions (6 patients, 13.4%). One patient underwent a gastric resection and three underwent diaphragmatic resections for local extension of their disease. All hilar cholangiocarcinoma patients underwent complete bile duct excision and portal lymphadenectomy with Roux-en-Y bilioenteric reconstruction. Cumulative warm ischemic time was 65 ± 24.5 minutes (range, 25–127 minutes). Total operating time (entering operating room to exiting) was 302 ± 88.6 minutes (range, 150–530 minutes). Mean CVP was 7.8 ± 3.2 cm H_2O (range, 2–13 cm H_2O).

There was no in-hospital mortality observed in this series. Twenty-nine patients (64.4%) had no perioperative complications. Complications are described

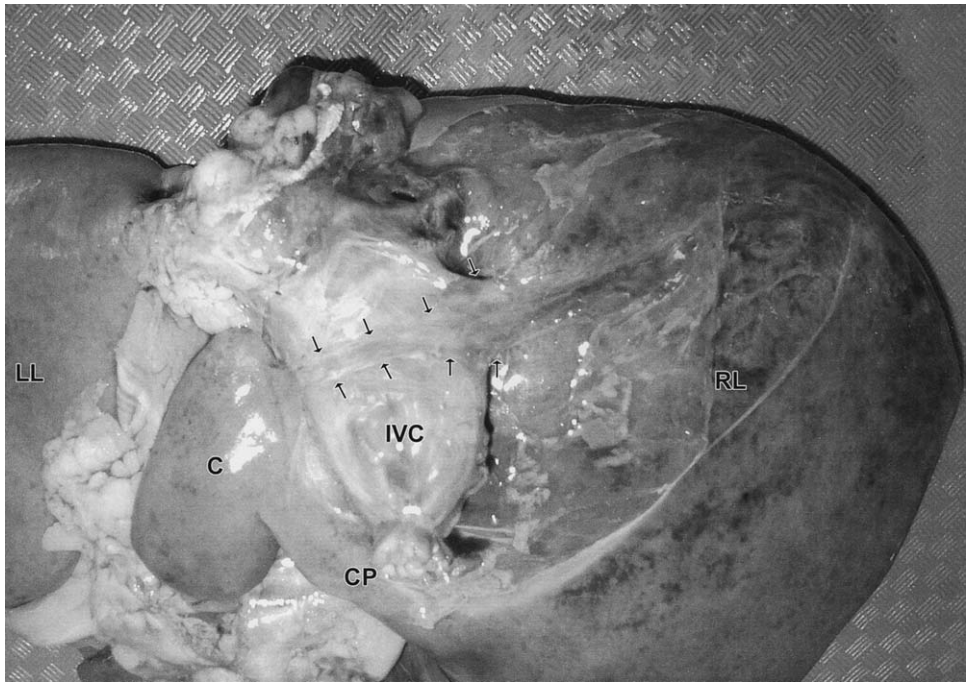

Fig. 5. Photograph of the posterior aspect of a cadaveric liver, demonstrating a type 1 hepatocaval ligament. The ligament is seen, between the *arrows*, as a wide band extending over the inferior vena cava from segment 7 of the right liver (RL) to the caudate lobe (C). It becomes narrower as it goes from right to left. LL = left liver, CP = caudate process.

in Table 1. One patient in whom we had failed to control the right hepatic vein had a self-limiting intraoperative air embolus. There was one major complication (grade 3): a subphrenic abscess requiring percutaneous drain insertion. No patients required reoperation. Peak ALT and bilirubin levels were 452 ± 420 U/L (range, 31–1685 U/L) and 42 ± 41 mmol/L (range, 8–189, mmol/L), respectively.

Eight (17.8%) patients received a blood transfusion of packed red blood cells (mean, 0.4 ± 0.2 unit; median, 0 units; range, 0–3 units) in the operative or perioperative period. No other blood products were given. The EBL was 864 ± 514 ml (range, 200–2500 ml). Two factors correlated with whether a blood transfusion was administered: the surgeon's perception of bleeding ($P = 0.0036$) and warm ischemic time ($P = 0.05$). Factors that did not correlate with incidence of transfusion included mean intraoperative CVP, resection type, selective vascular exclusion versus TVE, and patient demographics.

DISCUSSION

Our anatomic and clinical studies have clearly defined the anatomy of the hepatocaval ligament and hepatic veins and then demonstrated the utility of this information as it applies to a technique of liver resection—IHV-TVE. We demonstrated low morbidity, mortality, and transfusion rates associated with this technique. Further, liver damage was limited with the use of intermittent occlusion despite prolonged warm ischemic times.

The hepatocaval ligament is a vestige from the intrahepatic development of the superior portion of IVC and the hepatic vein from the right vitelline vein.[5] The hepatic origin of the ligament is supported by the fact that 12% of the ligaments are composed entirely of liver tissue and our histologic studies showing bile ducts in the ligamentous portions. Categorization of the hepatocaval ligament into three types based on its composition (i.e., amount of liver tissue present) helps to identify individuals in whom division of the ligament to expose the hepatic veins may be more difficult.

The right portion of the hepatocaval ligament must be divided to expose the origin of the right hepatic vein. An associated caudate vein (present in 69% of cases) requires control of the ligament with suture ligatures or clips to prevent inadvertent hemorrhage. Ramacciato et al.[6] recommended using a vascular endostapler to control an "inferior diaphragmatic vein" of significant dimension in the immediate vicinity of the ligament.

Couinaud[7] described a central space between the liver and the caudate lobe that is relatively avascular,

Table 1. Clinical series measures of patient outcome—mortality, complications, liver function, operative time, perioperative blood loss, and transfusions

Variable	n	Range
Death	0 (0%)	
Complication		
Major (grade 3) requiring intervention	1 (2%)	
Minor (grades 1, 2)		
Bile leak	2 (4.5%)	
Wound infection	8 (18%)	
Prolonged cholestasis	1 (2%)	
Upper respiratory tract infection	1 (2%)	
Air embolus	1 (2%)	
Intraoperative instability	2 (4.5%)	
	Total 16 (35.5%)	
Mean peak bilirubin (mmol/L)	42 ± 41	8–189
Mean peak ALT (U/L)	452 ± 420	31–1685
Mean warm ischemic time (min)	65.2 ± 24.5	25–127
Mean operating room time (min)	302 ± 88	150–580
Patients requiring transfusions (No.)	8 (17.8%)	1–3 units
Mean length of stay (days)	10.5 ± 3.5	5–23
Mean central venous pressure (cm H_2O)	7.8 ± 3.2	2–13.3
Mean postoperative hemoglobin (g/L)	109 ± 16	80–145
Mean blood loss Estimated (ml)	864 ± 514	200–2500

allowing the right hepatic vein to be dissected and encircled under direct vision. We also observed an absence of hepatic venous tributaries in this area of dissection and found that staying close to the hepatic veins avoids inadvertent injury.

A transient drop in blood pressure was occasionally noted during mobilization of the right liver. Potentially, the hypotension resulted in reduced venous return by flattening of the right hepatic vein and kinking of the IVC with retraction of the right liver. Makuuchi et al.[8] suggested that the hepatocaval ligament was responsible for kinking the IVC. We discovered that division of the hepatocaval ligament in cadaveric dissections did not alter this "kinking."

The common trunk of the middle/left hepatic vein has a limited extrahepatic course (90% <1 cm).[9] Based on the anatomic data from Chevallier[10] and Makuuchi et al.,[8] it is thought to be the most hazardous to dissect. Czerniak et al.[11] suggested that the middle and left hepatic veins must be taken separately, in their extrahepatic location. We found that the transverse orientation and more superficial plane of the common trunk allowed a reasonable dissection to encompass the entire vein trunk. The key maneuver is to develop a space cranial to the caudate lobe between the middle hepatic vein and the IVC. It has been suggested that the ligamentum venosum must be divided to perform this dissection. However, we found that when segments 2 and 3 are reflected superiorly, the ligamentum venosum is pulled out of the way, allowing dissection to proceed posteriorly. The space of Couinaud is also important for the dissection, as the plane of dissection passes through this space, anterior to the IVC. With this anatomic knowledge we were able to isolate this trunk 100% of the time.

TVE was first described by Heaney et al.[12,13] Occlusion of the suprahepatic and infrahepatic IVC during TVE can result in significant hemodynamic instability and may preclude its use in some patients.[14–16] Elias et al.[17] devised TVE with preservation of caval flow, where the portal triad and the hepatic veins are controlled in their extrahepatic location Our clinical series demonstrates outcomes consistent with those of the published literature[2,14,17–20] (Table 2): no mortality, no reoperations, and a complication rate of 35%.

It has been established that intermittent portal triad occlusion causes less liver damage than continuous occlusion.[21–24] Classic TVE is performed with continuous clamping, limiting its application. However, with control of the porta hepatus and hepatic veins with Rommel tourniquets TVE can be done intermittently, allowing longer liver warm ischemic times.[25] The exact safe length of this warm ischemia is not well established and may be different for cirrhotic livers.[26,27] Our mean warm ischemic time of 65 minutes with one patient extending out over 2 hours was long compared with the other series.[26,28] However, transaminase elevations were mild and none of our patients developed liver failure.

Ultimately, the primary goal of achieving control of hepatic inflow and outflow is the prevention of severe or catastrophic blood loss necessitating blood transfusions. Excessive intraoperative hemorrhage is associated with increased operative morbidity and mortality.[29–33] Moreover, blood transfusions are associated with immunosuppression, increased infection rates, and perhaps an increased rate of tumor recurrence.[34–37] By applying IHV-TVE, our mean EBL of 864 ml and our 18% transfusion rate compared favorably with other clinical series.[22,29,38] The main trigger for giving a blood transfusion appeared to be the surgeon's perception of blood loss (i.e., EBL).

Table 2. Summary of current literature for techniques of hepatic vein–total vascular exclusion

Study/Year	Patients enrolled	Patients with cirrhosis (n)	Death (%)	Complication (%)	Estimated blood loss (ml)	Transfusions (%)/ Unit mean (range)	Length of stay (mean days)	Warm ischemic time (min) (range)
Present study/2003	45	4	0	35.5	864 ± 514	17.8/0 (0–3)	10.5	65 (45–85)
Smyrniotis et al/2001	38	…	0	28.9	850 ± 700	…/3	16	32 ± 12
Cherqui et al/1999	40	16	0	17.5	…	30/0 (0–4)	10	27 (10–45)
Malassagne et al/1998	34	…	2	16.3	…	35/0 (0–4)	10	…
Leow et al/1996	18	15	0	…	2513	…	…	24.1 (10–35)
Elias et al/1995	16	4	6.25	37.5	1230	…	…	…
Cunningham et al/1994	100*	…	3	27	1180	67/…	13	…

*Veins for resection only.

However, none of our patients' postoperative hemoglobin levels dropped below 80 g/L. As it is now well established that a transfusion trigger of 70 g/L is appropriate,[39] we may have actually transfused too frequently.

Despite inflow and outflow occlusion, we still had almost a liter of blood loss with each major resection. We speculate that patients continued to bleed during parenchymal dissection for three reasons: (1) in many cases, the major caudate vein was not occluded, allowing blood to flow from the patent IVC; (2) reperfusion episodes refilled the hepatic vasculature, which subsequently bled during the next occlusive period; and (3) the CVP was not aggressively controlled (mean, 7.8 cm H_2O), allowing greater blood flow into the liver during reperfusion or via incompletely controlled hepatic veins. Clearly, using intermittent rather than continuous occlusion comes at a cost of more bleeding. While IHV-TVE appears to be effective in limiting blood loss, its major benefit may be in preventing catastrophic blood loss. Only four patients in our series had blood loss estimates greater than 2000 ml, usually the result of IVC injury.

In summary, an appreciation of the anatomy of the hepatocaval ligament and hepatic veins improves the safety of hepatic vein isolation. Control of the hepatic veins in conjunction with control of the porta hepatus has the potential advantages of TVE while avoiding the complications associated with IVC clamping.[2,14] We believe that the hybrid technique of IHV-TVE in which the hepatic veins and portal triad are occluded to prevent bleeding and this is done intermittently to prevent liver damage offers a reasonable compromise between bleeding and warm hepatic ischemia.

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Is Routine Placement of Surgical Drains Necessary After Elective Hepatectomy? Results From a Single Institution

Ali Aldameh, M.B.Ch.B., John L. McCall, M.D., F.R.A.C.S., Jonathan B. Koea, M.D., F.R.A.C.S.

Routine drainage is no longer used after many major abdominal procedures. However, the role of routine surgical drainage after hepatic resection is unclear. Of the two randomized trials published, one concluded drainage is unnecessary after hepatectomy, and another concluded it could be used after major resections only. Between January 1999 and December 2003, 211 elective hepatic resections were performed by two surgeons at Auckland Hospital. Drains were used routinely by one surgeon (n = 126), while another routinely did not drain (n = 85). Patients undergoing a biliary reconstruction were not included in this analysis. Patient and clinical data were recorded prospectively, and no outcome analyses were performed until 2004. The demographic features were similar between the drained and nondrained groups. There were no differences in length of hospital stay (no drain, 7 ± 0.8 days; drain, 7 ± 0.9 days: P = not significant [NS]), in mortality (no drain, 1.2%; drain, 1.6%: P = NS), biliary fistula (no drain, zero cases; drain, two cases: P = NS), or overall complication rate (no drain, 50.5%; drain, 54.7%: P = NS). Both groups had similar rates of postoperative collection (no drain, four patients [5%]; drain, five patients [4%]: P = NS), and there was no difference in the use of percutaneous drainage of collections between the groups (no drain, four patients [5%]; drain, two patients [2%]: P = NS). Multivariate analysis showed that intraoperative blood loss of 2000 ml or greater (relative risk [RR], 1.57; 95% confidence interval [CI], 1.39-1.75; $P < 0.01$), number of segments resected (RR, 1.4; 95% CI, 1.21–1.89; $P < 0.01$), and presence of steatosis/fibrosis or cirrhosis (RR, 1.6; 95% CI, 1.01–2.1; $P < 0.05$) to be predictive of postoperative complications. The presence of a surgical drain was not predictive of complications. Routine surgical drainage after elective hepatectomy is not necessary. (J GASTROINTEST SURG 2005;9: 667–671)

KEY WORDS: Hepatectomy, biloma, surgical drain

The placement of surgical drains at the end of an operative procedure was once considered obligatory because surgical drains were thought to facilitate the diagnosis of postoperative bleeding and to reduce the risk of postoperative fluid collections by allowing intra-abdominal fluid to track to the skin surface. However, there is increasing evidence that routine placement of surgical drains does not decrease the rate of postoperative complications after a number of procedures, including neck exploration,[1] cholecystectomy,[2] colonic resection,[3] and in pediatric surgery.[4] In addition, it is now appreciated that surgical drains can cause complications[5,6] and may act as conduits for infection. Consequently, drains are no longer used routinely after many surgical procedures.

The role of surgical drains after elective hepatectomy is less clear. Two randomized trials have been published examining the use of drains after elective hepatectomy. The trial by Fong et al.[7] concluded that abdominal drainage was unnecessary after elective hepatic resection, whereas the trial of Belghiti et al.[8] concluded that drainage was unnecessary after minor liver resections but that it could be used after major hepatic resections. A number of prospective series have also been published either supporting[9] or

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From the Upper Gastrointestinal/Hepatobiliary Unit, Department of Surgery, Auckland Hospital, Auckland, New Zealand.
Reprint requests: Jonathan Koea, M.D., F.R.A.C.S., Department of Surgery, Auckland Hospital, Private Bag 92024, Auckland, New Zealand. e-mail: jonathank@adhb.govt.nz

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refuting[10] the routine use of drains after elective hepatectomy.

Because of this uncertainty in the literature surrounding the role of surgical drainage in elective hepatectomy, our unit investigated the concept of carrying out an eventual prospective randomized trial of surgical drainage after elective hepatectomy. As part of this process, a combined retrospective and prospective audit of our experience with drainage after hepatectomy was undertaken, and the results of this review form the basis of this report. The specific aim of this investigation was to examine the role of routine intra-abdominal drainage on the development and treatment of postoperative complications after elective hepatectomy.

METHODS

A prospective computerized database of patients managed by the Upper Gastrointestinal/Hepatobiliary Unit at Auckland Hospital was established in 2000. Demographic, clinical, pathologic, management, and follow-up data are recorded prospectively on all patients managed by the unit. Review of the database identified 211 patients who had undergone elective hepatic parenchymal resection at Auckland Hospital between January 1998 and December 2003. No patient with a biliary anastomosis was included, and the data set comprised only those patients who had undergone resection of hepatic parenchyma only. Resections were classified according to the nomenclature proposed by the International Hepato-Pancreato-Biliary Association[11] with major liver resections being those encompassing four or more hepatic segments, whereas minor resections were those that removed fewer than four hepatic segments.

Hepatic resections at Auckland Hospital are carried out by two surgeons. One surgeon had a policy of routine drainage in all cases (n = 126 patients within the study period using a closed nonsuction drainage system in all cases). This system comprised an 18 Fr drainage tube connected to a bag using gravity for drainage. The other surgeon had a routine policy of nondrainage in all cases (n = 85 patients within the study period).

In analyzing outcome after hepatectomy, we were specifically interested in complications related to the presence of an intra-abdominal collection because control of postoperative collections is a primary reason for placement of drains. In this investigation, a biloma was defined as an intra-abdominal fluid collection containing bile, whereas a bile fistula was defined as drainage of more than 50 ml of bile per day for longer than 3 days from the abdominal cavity. An infected collection was defined as a non–bile-containing fluid collection with organisms present on culture.[12]

Statistical analysis was carried out using Fisher's exact test for comparisons between the drained and nondrained groups. A χ^2 test was used to define significant prognostic factors on univariate comparison. Using multiple logistic regression in the SPSS statistical package (SPSS, Chicago, IL), prognostic factors were determined for the hazard rate of complications. Differences were considered significant at the $P = 0.05$ level, and all deaths within 60 days of surgery were treated as surgical mortality.

RESULTS

Demographics

A total of 211 patients were entered in this study: 126 were drained and 85 were not drained. There were no differences in the demographic features between the drained and nondrained groups (Table 1). The majority of liver resections in our unit were performed for metastases from colorectal cancers (n = 108, 56%). Hepatocellular carcinoma constituted 9% of the patients (n = 20). The distribution of the tumor types and indications for resection was similar among patients operatively drained and patients not drained (Table 2). One hundred eleven patients (53%) required the resection of a lobe or more.

Outcome

For none of the parameters studied was there a difference in outcome (Table 3). Approximately half of the patients in the drained and nondrained groups developed complications (Table 3), with 69 complications occurring in 50 patients in the drain group, whereas 43 complications occurred in 32 patients in the nondrain group (40% versus 38%). Only the relative incidence of wound infections approached

Table 1. Demographic details of patients with and without drainage following elective hepatic resection

	Drain (n = 126)	Nondrain (n = 85)	*P* Value
Gender (M/F)	60/66 (48%/52%)	30/55 (35%/65%)	0.4
Age (median, range)	60 (4–81)	61 (1–84)	0.7
Major resection	79 (63%)	32 (38%)	0.6
Minor resection	47 (37%)	53 (62%)	0.5

Table 2. Indications for elective hepatic resection in 211 patients

	Drain (n = 126)	Nondrain (n = 85)
Cholangiocarcinoma	3 (2%)	5 (6%)
Colorectal cancer (CRCa) metastasis	71 (57%)	38 (45%)
Gallbladder cancer	2 (1%)	7 (8%)
Hepatic adenoma	3 (2%)	4 (5%)
Hepatocellular carcinoma	16 (13%)	4 (5%)
Hydatid cyst	1 (1%)	2 (2%)
Neuroendocrine (NE) metastasis	4 (3%)	5 (6%)
Non-CRCa–non-NE metastasis	4 (3%)	8 (9%)
Others*	22 (18%)	12 (14%)

*These include focal nodular hyperplasia and benign biliary strictures.

significance, with a higher rate observed in the nondrained group (Table 3). There were two deaths in the drained group and one death in the nondrained group (2% versus 1%), and hospital stay was similar in both groups (7 ± 0.9 days versus 7 ± 0.8 days).

Major Versus Minor Hepatectomy

Analysis of the outcomes was also undertaken for major (four or more segments resected) versus minor resections (less than four segments resected). There was no difference noted between the complication rates for minor and major resections when the results were stratified for the presence or absence of surgical drains (Table 4).

Risk Factors for Postoperative Complications

On univariate analysis, the extent of parenchymal resection, intraoperative blood loss, and the presence of abnormal hepatic parenchyma (fibrosis, steatosis, or cirrhosis) were found to be associated with and increased risk of complications (Table 5). On multivariate analysis, intraoperative blood loss of 2000 ml or more (RR, 1.57; 95% confidence interval [CI], 1.39–1.75; $P < 0.01$), four or more segments resected (RR, 1.4; 95% CI, 1.21–1.89; $P < 0.01$), and the presence of abnormal parenchyma (RR, 1.6; 95% CI, 1.01–2.10; $P < 0.05$) were also predictive of postoperative complications.

Table 3. Postoperative complications, hospital stay, and postoperative percutaneous drainage in the elective hepatic resection

	Drain (n = 126)	Nondrain (n = 85)	*P* Value
Mortality	2 (2%)	1 (1%)	0.8
Total complications	69 (53%)	43 (51%)	0.3
Hepatic failure	7 (6%)	1 (1%)	0.1
Infected collection	3 (2%)	1 (1%)	0.4
Bile collection	2 (2%)	3 (3%)	0.5
Biliary fistula	2 (2%)	0	0.6
Wound infection	8 (6%)	14 (16%)	0.09
Percutaneous drainage	2 (2%)	4 (5%)	0.2
Median hospital stay (days)	7 ± 0.9	7 ± 0.8	0.7

DISCUSSION

This investigation was undertaken to review our unit's experience of surgical drainage after elective hepatectomy as a prelude to the development of a randomized trial. Although no differences in outcome were identified between drained and nondrained patients, this study was retrospective and nonrandomized and the results may be confounded by a number of factors. Differences between the surgeons could have obscured real differences in drain-related outcomes. The retrospective nature of the study means that drain-related complications may not have been identified, although it is much less likely that major complications would have been overlooked because a comprehensive, prospective database was maintained from 2000 on. There was certainly no evidence of a difference in major complications. If anything, this study may have underreported more minor drain-related complications, such as drain site discomfort or cellulitis. Overall, it does not provide any evidence to suggest that not using a drain is harmful. Based on the results of this investigation, routine surgical drainage after elective hepatectomy is no longer used by our unit. While there are only two published randomized trials of drainage versus no-drainage after elective hepatectomy, it would appear that no further randomized trial is necessary given the findings of the current study as well as those of others.[7,8,10]

This experience is consistent with that of other units. In a nonrandomized, prospective study, Franco et al.[10] reported 61 hepatic resections without drainage; the authors concluded that drainage was unnecessary after hepatic resection. In a similar study Bona et al.[9] reached the opposite conclusion because they were unable to demonstrate that surgical drains had an adverse effect on patient outcome. However, both of the two published randomized trials[7,8] of surgical drainage after hepatectomy reported a higher rate of septic complications in the drained group, demonstrating that surgical drainage does carry a discrete morbidity, and Fong et al.[7] concluded that routine surgical drainage after hepatectomy is unnecessary.

Table 4. Complication rates for major hepatic resections (≥4 hepatic segments resected) versus minor hepatic resections (<4 segments resected) in drained and undrained patients

	Major resections (n = 111)			Minor resections (n = 100)		
	Drain (n = 79)	Nondrain (n = 32)	*P* Value	Drain (n = 47)	Nondrain (n = 53)	*P* Value
Mortality	2 (2%)	1 (3%)	0.4	—	—	—
Abdominal collection	4 (5%)	2 (6%)	0.5	3 (6%)	2 (4%)	0.7
Percutaneous drainage	2 (2%)	1 (1%)	0.6	—	3 (6%)	0.4
Wound infection	4 (5%)	5 (15%)	0.8	4 (8%)	9 (17%)	0.3
Total complications	52	16	0.1	17	27	0.5
Median hospital stay (days)	7.2	7.2	0.9	6.4	6.8	0.6

It is interesting to note that the wound infection rate was higher in the nondrained patients in this series and that this difference approached statistical significance. The clinical significance of this observation is unclear. As drained and nondrained patients were managed by two surgeons, it is possible that the diagnosis of wound infection varied between the two caregivers. Alternatively, nondrained patients may be more at risk of developing infectious complications of the wound.

In the trial of Belghiti et al.,[8] 81 patients were randomized into drained (n = 42) or nondrained (n = 39) groups. A higher rate of complications occurred in the drained group; however, the majority of liver resections in this analysis were minor resections. Therefore, Belghiti et al. concluded that minor liver resection is safer without drainage and that major resection can be performed with or without drainage. Because of this issue and the fact that it could be argued that patients with minor liver resections are more likely to experience postoperative complications[13] and require drainage, we specifically analyzed our data in terms of minor versus major hepatectomies and found no indication for increased use of drains in either group. Our results therefore agree with those of Fong et al.[7,14]

We have previously reported that up to 50% of patients undergoing hepatectomy will experience complications, with the vast majority being minor and non–life-threatening.[15] This investigation reinforces the finding that the risk of complications in elective hepatectomy is directly related to the presence of cirrhosis, steatosis, or fibrosis in the specimen; the extent of the resection; and the development of major intraoperative hemorrhage.[16] Placement of surgical drains does not protect against the development of postoperative complications after elective hepatectomy, and because it may be associated with a small but significant morbidity,[7,8] its routine use cannot be recommended.

Table 5. Risk factors for complications following hepatectomy in drained and undrained patient groups (univariate analysis)

	Complication	No complication	*P* Value
Surgical drainage			
No	43	42	0.7
Yes	69	57	
≥4 Segments resected			
No	44	56	<0.01
Yes	68	43	
Blood loss ≥2000 ml			
No	97	93	<0.01
Yes	15	6	
Abnormal parenchyma			
No	73	97	<0.01
Yes	39	2	

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Impact of Aberrant Arterial Anatomy and Location of Anastomosis on Technical Outcomes After Liver Transplantation

Marwan S. Abouljoud, M.D., Dean Y. Kim, M.D., Atsushi Yoshida, M.D., Juan Arenas, M.D., John Jerius, M.D., Lauren Malinzak, M.D., Mohammad Raoufi, M.D., Kimberly A. Brown, M.D., Dilip K. Moonka, M.D.

Variations in donor and recipient arterial anatomy frequently present challenges for surgeons when attempting to establish proper arterial inflow during liver transplantation. We reviewed our data on 233 adult primary liver transplants, conducted from January 1996 through December 2001, to determine the impact of these variations on the outcomes after liver transplantation. Twenty-four (10.3%) arterial complications were encountered at a mean of 2.27 months after transplant. Carrel patches for the anastomoses were not used in 33 patients (14%), which had no relation to arterial complications ($P = 0.7$). Sixty-one donors (26.2%) had at least one aberrant artery, which had no relation to arterial complications. However, use of donor celiac artery for anastomosis was significantly associated with higher arterial complications (16% versus other choices, $P = 0.03$). Furthermore, use of common hepatic recipient artery was associated with higher arterial complications (16%, $P = 0.03$). There were 58 total biliary complications (24.8%). Biliary complications were associated with the presence of arterial complications ($P = 0.01$). In conclusion, aberrant donor arterial anatomy was not associated with an increased rate of arterial complications; however, choice of location of arterial anastomosis may be a significant factor. Biliary complications were associated with arterial complications. (J GASTROINTEST SURG 2005;9:672–678)

KEY WORDS: Liver transplantation, postoperative complications, hepatic artery, bile ducts

INTRODUCTION

Orthotopic liver transplantation (OLT) has become standard therapy for selected patients suffering from complications of end-stage liver disease. The success of this procedure has improved with better immunosuppression and surgical techniques. Variations in donor and recipient arterial anatomy frequently present challenges for the surgeon when attempting to establish proper arterial inflow. Such anatomical variations have been reported in 24.3% to 42.2% of all donor livers.[1–3] Previous reports have noted an increased incidence of arterial complications when aberrant arterial anatomy was present,[4] although more recent data suggest no difference unless multiple anastomoses were required.[2] In this study we examine our experience with aberrant arterial anatomy and the impact of various technical details on the outcome of the arterial anastomoses. In addition, we examine the relationship between the presence of such anatomical variations and biliary complications.

MATERIAL AND METHODS

Adults undergoing primary OLT between January 1996 and December 2001 were reviewed for this study. Data on surgical anatomical details were prospectively collected. Medical records were reviewed for outcomes and morbidities. Data included donor and recipient arterial anatomy and choice of inflow vessels, need for arterial reconstruction, use of a Carrel patch to perform the arterial anastomosis, need

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From the Henry Ford Transplant Institute, Henry Ford Hospital, Detroit, Michigan.
Reprint requests: Dean Y. Kim, M.D., Division of Transplantation Surgery, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202. e-mail: dkim3@hfhs.org

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for arterial conduits, and the presence of biliary complications. Follow-up ranged from 1 to 6 years.

Technical Details

Early in this experience, the donor celiac trunk on an aortic patch was the preferred vessel (Fig. 1) and was typically anastomosed to the recipient proper hepatic artery (Fig. 2*A*) or common hepatic artery (Fig. 2*B*) on a branch Carrel patch. We have subsequently favored using the donor common hepatic artery on a branch Carrel patch (Fig. 3*A* and *B*). When a branch Carrel patch was not possible, the vessel was spatulated for a direct end-to-end anastomosis. When an aberrant right hepatic artery was noted, in most situations arising from the superior mesenteric artery (Fig. 4*A*), it was managed with reimplantation into the stump of either the gastroduodenal artery (GDA) or splenic artery (Fig. 4*B*). An aberrant left hepatic artery was never reimplanted in this series. On occasion, the recipient hepatic artery was not suitable for anastomosis. In these cases, either the splenic artery or the aorta was used as the inflow vessel, with a conduit of donor iliac artery if needed. Biliary anastomoses were routinely done over 5 F internal stents. Duct-to-duct anastomoses were favored unless otherwise dictated by disease or technical factors, when a Roux-en-Y choledochojejunostomy would be performed.

Doppler ultrasound of the liver and/or liver biopsy was performed when elevated liver function tests (SGOT, SGPT, alkaline phosphatase, and bilirubin) were determined on routine follow-up. A diminished resistive index (compared to baseline) or blunted waveform (parvus tardus) was an indication for an arteriogram. Findings on liver biopsy suggestive of liver ischemia (e.g., necrosis, zone three ballooning) also was an indication for an arteriogram. A significant arterial stenosis was diagnosed when intervention was needed to improve flow in the appropriate clinical setting. Similarly, a bile duct complication was noted when an intervention was needed to repair a finding of either a leak or a stricture.

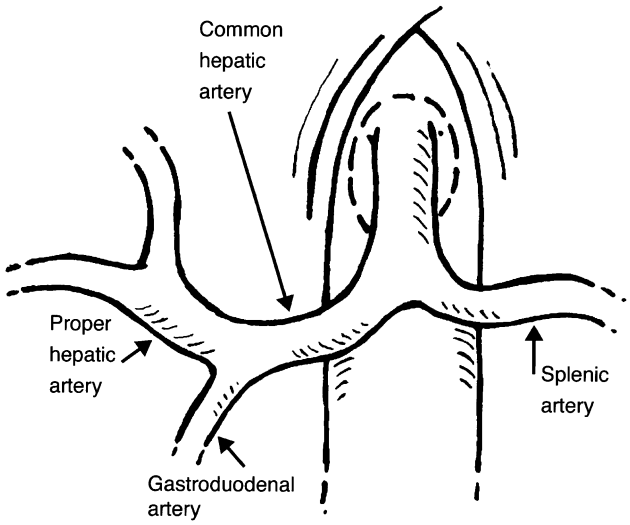

Fig. 1. Donor celiac trunk. The dashed line indicates the cuff of aorta taken along with the donor celiac trunk during procurement.

χ^2 test and post hoc analyses with the Fisher's exact test, where appropriate, were used. Pearson correlation was also used where appropriate. A P value of <0.05 was considered statistically significant. Univariate analyses of the data were performed for this study because there were limited numbers of complications to review. Statistical analyses were performed using a statistical software package, NCSS 2000 (Number Cruncher Statistical Systems, Kaysville, UT). The study protocol was approved by the Henry Ford Hospital Institutional Review Board.

RESULTS

Two hundred thirty-three patients with a mean age of 50.1 ± 10.1 years underwent primary OLT during the study period. Seventy-six were women (32.5%) and 157 were men (67.5%). Donor arterial anatomy was categorized into five groups: normal, accessory right, accessory left, both, and total replaced (Table 1). There were 61 (26.2%) situations in which aberrant anatomy was noted.

Arterial complications occurred in 24 patients (10.3%), including hepatic artery stenosis (16 patients, 6.8%), thrombosis (7 patients, 3%) and pseudoaneurysm (1 patient, 0.4%). Arterial complications occurred at a mean of 2.27 months and a median of 1.23 months after transplant, with a range of 1 day to 7 months. There was no association with recipient sex ($P = 0.5$). Nineteen of the complications occurred in patients with normal donor anatomy, three in those with an aberrant left hepatic artery, one in a donor with an aberrant right hepatic artery, and one in a donor with both aberrant right and left hepatic arteries. There was no relationship between donor anatomy and the development of an arterial complication ($P = 0.75$), even when subgroups with aberrant anatomy were combined as one group ($P = 0.63$), and no relationship between the need for a reconstruction (when an aberrant right hepatic artery was present) and the development of an arterial complication ($P = 0.65$). A breakdown of arterial complications by donor anatomy is also illustrated in Table 1.

A Carrel patch was used in 201 patients (85.9%), while a direct end-end anastomosis was used in 33

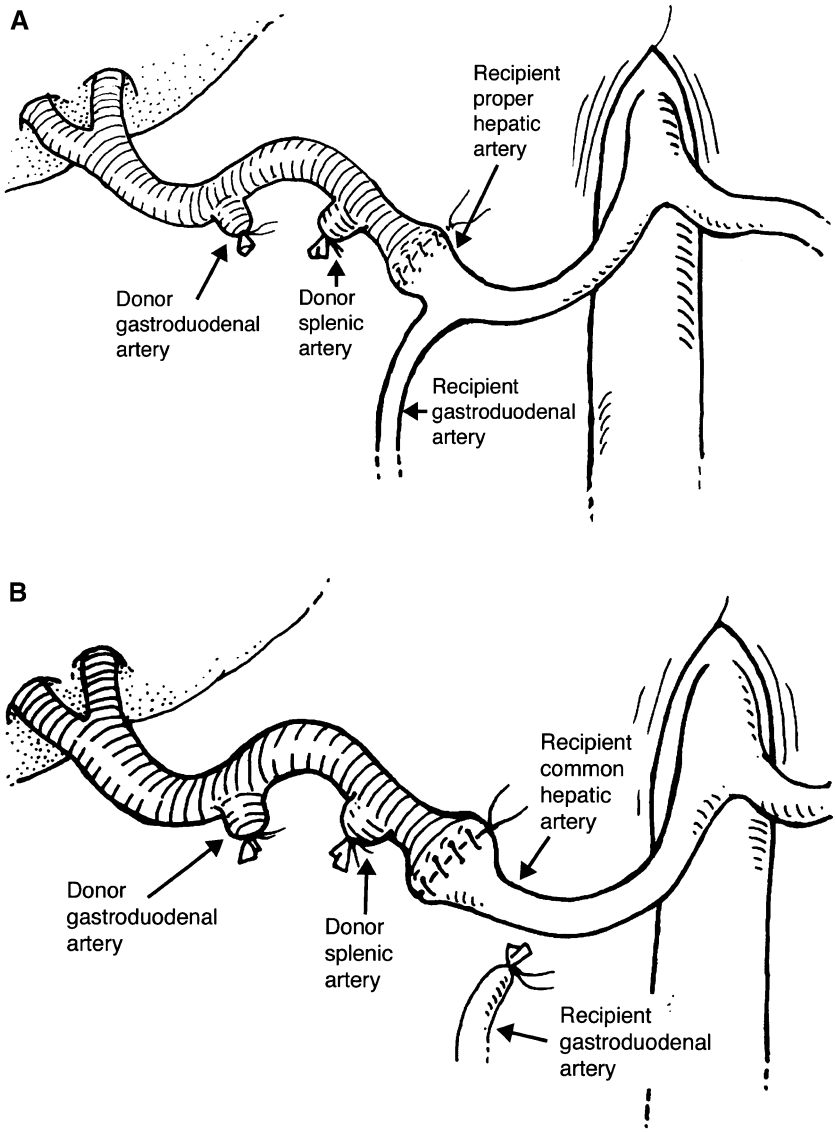

Fig. 2. (**A**) Donor celiac trunk (represented by the striped vessel) anastomosed to the recipient proper hepatic artery. The recipient right and left hepatic arteries are spatulated to create a Carrel patch for the anastomosis. (**B**) Donor celiac trunk (represented by the striped vessel) anastomosed to the recipient common hepatic artery. The recipient GDA is ligated and a Carrel patch is created for the anastomosis.

patients (14.1%). The rate of arterial complications was comparable between these groups (12% with patch vs. 10% without, $P = 0.76$). There were 10 patients who required arterial conduits. Seven conduits were from the aorta and the remaining three were from the splenic artery. Two patients with conduits developed arterial complications. There was no significant difference between the patients who required conduits and those who did not ($P = 0.27$), although the numbers were small.

In order to further define possible etiologies for the observed arterial complications, we examined the donor and recipient arteries chosen for anastomosis. Choice of donor artery and associated arterial complications is illustrated in Table 2. The incidence of complications was higher in the celiac group (n = 12, 15.8%), which accounted for half of all arterial complications ($P = 0.03$). We then looked at the choice of recipient artery, detailed in Table 3. The recipient common hepatic artery was associated with a higher arterial complications rate (16.1%) when compared with the hepatic artery proper (6.6%) ($P = 0.03$).

There were 56 (23.9%) biliary complications overall that required intervention. Of these, there were 36 strictures (1 intrahepatic), and 20 biliary leaks (3 associated with early extensive duct necrosis and hepatic artery thrombosis). There was a significantly

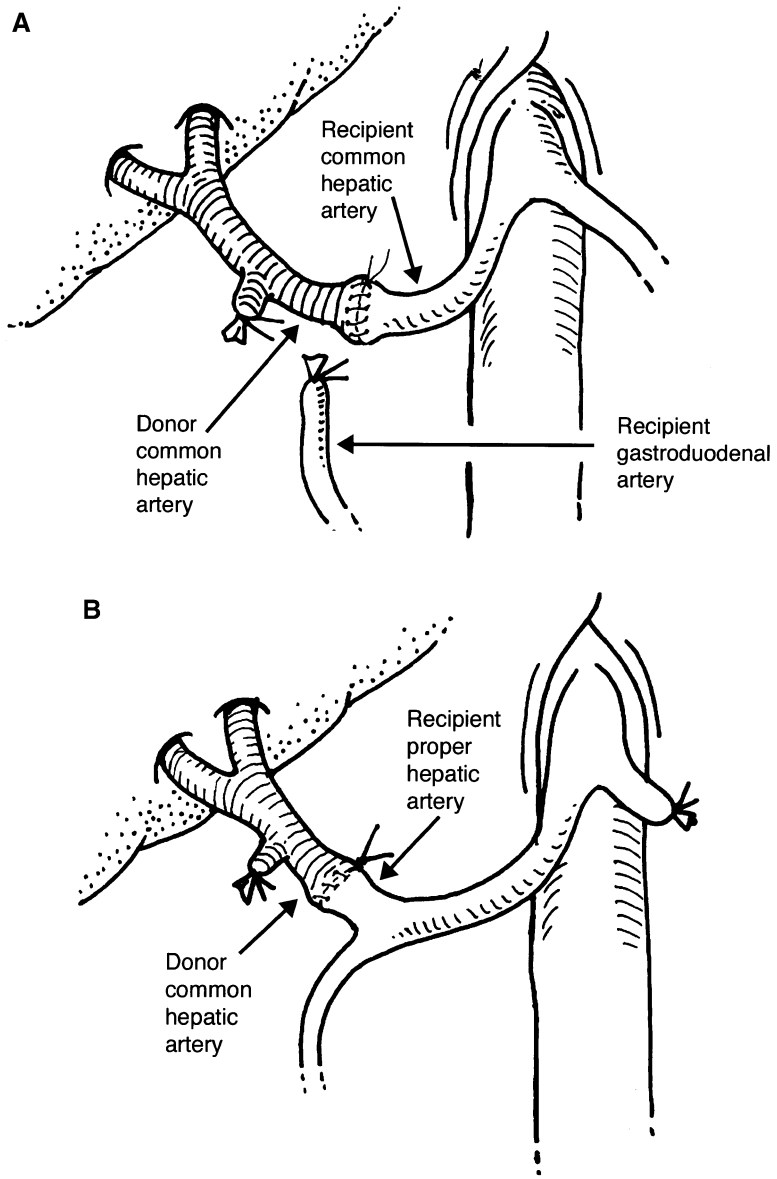

Fig. 3. (**A**) Donor common hepatic artery (represented by the striped vessel) anastomosed to the recipient proper hepatic artery. The recipient right and left hepatic arteries are spatulated to create a Carrel patch for the anastomosis. (**B**) Donor common hepatic artery (represented by the striped vessel) anastomosed to the recipient common hepatic artery. The recipient GDA is ligated and a Carrel patch is created for the anastomosis.

higher incidence of biliary complications in patients with arterial complications (11/24, 45.8%), compared with those without arterial complications (47/210, 22.4%) ($P = 0.01$).

DISCUSSION

The potential for morbidity and mortality with arterial complications after liver transplantation is substantial,[5] and knowledge of associated risk factors and prevention strategies is essential. It has been reported previously that donor arterial anomalies may be associated with a higher incidence of arterial complications.[4] However, the present study and those of others do not confirm this.[1,2,6] The reasons may be multifactorial, including improved surgical technique and organ preservation.

Soin et al.[2] noted a 30.6% incidence of anomalous arterial anatomy among donors. In addition, they noted a similar incidence of biliary complications (18.0%) among such patients, compared with those with normal anatomy (18.8%). However, they

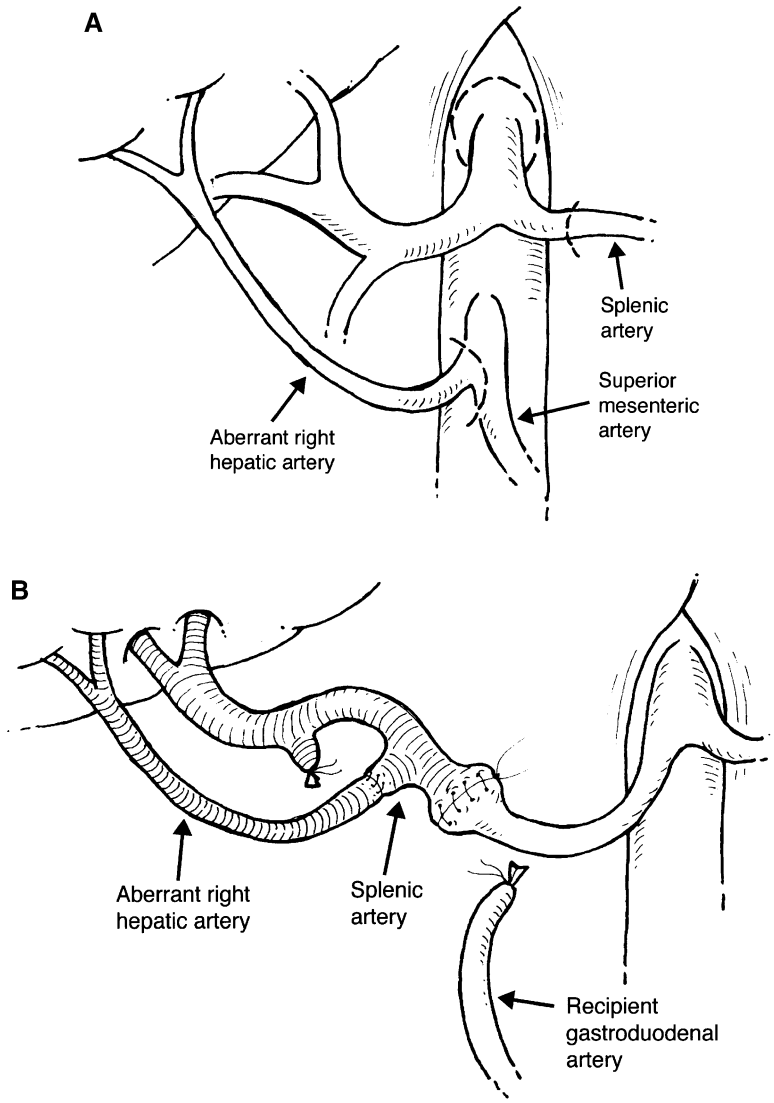

Fig. 4. (**A**) Donor celiac trunk with an aberrant right hepatic artery. The aberrant right hepatic artery usually takes off of the superior mesenteric artery. The dotted circle indicates the aortic cuff taken during the procurement. The dotted arc indicates where the splenic artery is divided. (**B**) The aberrant right hepatic artery is usually anastomosed to the donor splenic artery stump (represented by the striped vessels) and then the celiac trunk is anastomosed to the recipient common hepatic artery. The recipient GDA is ligated and a Carrel patch is created for the anastomosis. Sometimes, instead of anastomosing the aberrant right hepatic artery to the donor splenic artery stump, it is anastomosed to the donor GDA stump (ligated in this picture).

described a significant increase in arterial complications when one or more reconstructions were needed or when a conduit was used for direct aortic inflow, which was not noted in our series. The "era" of transplantation has also been studied in relation to hepatic artery complications.[7] This group reported a 4.5-fold increase in hepatic artery thrombosis in the pre-1990 era compared to the subsequent era. In addition, they found no negative impact with the use of aortic conduits, although a 2.5-fold increase in hepatic artery thrombosis occurred when a direct anastomosis was done without a Carrel patch. The positive impact of using a Carrel patch has also been previously described.[6,7] Our experience does not show that there is much difference among these groups, most likely because of the use of fine surgical techniques, proper magnification, and interrupted fine sutures. However, vessel caliber and method of performing the direct end-to-end anastomoses have not been detailed in most series. Consistent use of intraoperative hepatic artery flow measurements may have aided in the reduction of early hepatic artery events in such

Table 1. Distribution of various donor arterial anomalies and arterial complications

Donor anatomy	n (%)	No. of complications (%)
Normal	172 (73.8)	19 (79.2)
Aberrant right	30 (12.9)	1 (4.2)
Aberrant left	19 (8.2)	3 (12.5)
Aberrant right and left	10 (4.3)	1 (4.2)
Total replaced	2 (0.8)	0
Total	233	24

Table 3. Recipient artery used for arterial anastomosis and arterial complications

Recipient artery	n (%)	No. of complications (%)
Hepatic artery proper	122 (52.4)	8 (33.3)
Common hepatic	87 (37.3)	14 (58.3)
Replaced right hepatic	13 (5.6)	1 (4.2)
Aorta	7 (3.0)	1 (4.2)
Left hepatic	3 (1.3)	0 (0)
Splenic	1 (0.4)	0 (0)
Total	233	24

patients in our series as well. Although data is somewhat limited, one group did describe the benefit of intraoperative hepatic artery flow measurements as a possible predictor of early hepatic artery thrombosis/stenosis.[8]

The impact of the artery chosen for inflow or outflow has not been examined in detail previously. Our standard technique predominantly required the use of the donor celiac artery on an aortic patch and the recipient common hepatic artery with a branch Carrel patch. As we observed a higher than expected incidence of post-anastomotic stenosis, we modified the technique to preferentially use the donor common hepatic artery on a branch Carrel patch. Our results support the fact that the use of the donor celiac trunk was associated with a higher rate of arterial complications (15.8%). We believe that this is, in part, caused by flow dynamics among vessels of different caliber and wall stiffness and shear stress. The latter, along with the shape of the anastomosis, may impact flow patterns significantly. This change in flow dynamics has been demonstrated to influence the development of intimal hyperplasia.[9] The association of recipient common hepatic artery with hepatic artery complications was not an expected finding in the present study. We hypothesize that this is related to our working algorithm as we proceed with intraoperative choices. We typically favor the recipient hepatic artery proper; if the latter is not of good caliber, then the common hepatic artery proximal to the gastroduodenal artery is chosen. This may suggest a negative bias in terms of vessel caliber, extent of dissection, and ease of performing a proper anastomosis. In future transplants, we will make an effort to record the reason for choosing this and other vessels to aid further in understanding this finding. However, because this was a retrospective study, it is difficult to determine whether the improved results were secondary to improved surgical technique or whether the outcomes were based on the artery chosen for anastomoses.

Table 2. Donor artery used for arterial anastomosis and arterial complications

Donor artery	n (%)	No. of complications (%)
Common hepatic	129 (55.4)	8 (33.3)
Celiac	76 (32.6)	12 (50.0)
Superior mesenteric	14 (6.0)	0 (0)
Hepatic artery proper	8 (3.4)	2 (8.3)
Right hepatic	5 (2.1)	1 (4.2)
Splenic	1 (0.4)	1 (4.2)
Total	233	24

In our experience, an association between bile duct complications and aberrant arterial anatomy was not found. This was not surprising; the incidence of arterial complications was not higher in patients with aberrant donor arterial anatomy. However, a significant association was noted between the presence of arterial complications and bile duct complications, as noted by others.[10,11] In the practice setting, the presence of a biliary complication, especially in the early postoperative period, should dictate a thorough assessment of the hepatic arterial flow. In our series, 45.8% of patients with arterial complications developed a biliary complication requiring intervention, compared with 22.4% in patients without an arterial problem.

There are two limitations of the present study. The first was that this was a retrospective analysis of a single center experience in liver transplantation. Although programmatic changes were implemented in order to improve outcomes, results of the analyses will inevitably have selection biases. Second, because there were relatively small numbers of arterial and biliary complications, we were unable to perform multivariate analyses of our data, which may potentially lead to confounding results.

CONCLUSION

With improved surgical expertise and better organ preservation and immunosuppression, the presence of aberrant arterial anatomy does not have a major

impact on arterial complications after orthotopic liver transplantation. However, choice of vessel for reconstruction may influence outcome. The association between the presence of biliary and arterial complications is consistent, and a detailed work-up should be conducted when either is present.

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Postoperative Severe Microangiopathic Hemolytic Anemia Associated With a Giant Hepatic Cavernous Hemangioma

Kaysie L. Banton, M.D., Jonathan D'Cunha, M.D., Ph.D., Noel Laudi, M.D., Catherine Flynn, M.D., Dale Hammerschmidt, M.D., Abhinav Humar, M.D., Timothy Sielaff, M.D., Ph.D.

Complications related to liver hemangioma are rare. We herein describe the case of a patient with three giant cavernous hemangiomas of the liver, of which two were resected for symptoms. A significant microangiopathic hemolytic anemia occurred in the early postoperative period, leading to acute renal failure and necessitating blood transfusions. The systematic evaluation of hemolytic processes in the postoperative patient is described. Surgeons should be aware of the potential for hemolytic complications after major surgery when giant hepatic hemangiomas are present. (J GASTROINTEST SURG 2005;9:679–685)

KEY WORDS: Cavernous hemangioma, microangiopathic hemolytic anemia, postsurgical complication

Hemangiomas are the most common benign tumor of the liver, with a frequency of 0.4–20% worldwide.[1–5] The female-to-male ratio is 3:1.[4,6,7] Small capillary hemangiomas are certainly more common, but giant cavernous hemangiomas (>4 cm) can be of surgical importance.[5,8,9] Hemangiomas are considered to be vascular malformations because they enlarge through ectasia and have no malignant potential.[1,3] They most commonly occur as solitary lesions; however, liver hemangiomas occur as multiple lesions up to 40% of the time.[3,7] In patients who are followed over the long term, the vast majority of the hemangiomas remain stable over time.[4] The overall risk of intra-abdominal hemorrhage is low (estimated at <1%).[5] Therefore, surgical resection is reserved for the treatment of symptoms such as aggressive growth, local discomfort, and early satiety.[1,6]

Hematologic complications of liver hemangiomas are rare and include hemorrhage secondary to consumptive coagulopathies such as disseminated intravascular coagulation (DIC),[10–12] Kasabach-Merritt syndrome,[13–15] microangiopathic hemolytic anemia (MAHA)[12,14,16–22] and Budd-Chiari syndrome.[21] We herein describe the case of a patient with MAHA due to a giant hemangioma that occurred after a major surgical procedure.

CASE REPORT

The patient is a 54-year-old woman with a long-standing history of multiple giant hemangiomas of the liver. In the 12 months before surgery, she developed progressive symptoms of early satiety and unrelenting, disabling midabdominal pain (sharp and episodic). Her past medical history was significant only for hypertension. Her medications included irbesartan, hydrochlorothiazide, and amlodipine. She had never used tobacco and had no history of blood transfusions or previous surgery. Her family history was not significant.

Examination revealed a soft abdomen that was grossly distorted from a palpable right-upper-quadrant mass extending into the pelvis. No abdominal bruit was noted. Her preoperative laboratory test results were as follows: hemoglobin 11.0 g/dL, platelets 241×10^9 per liter, INR 1.0, and serum creatinine 0.84 mg/dL. Abdominal computed tomography (CT) with oral and intravenous contrast disclosed several

From the Departments of Surgery (K.L.B., J.D., A.H.) and Medicine (N.L., C.F., D.H.) University of Minnesota Medical School and the Virginia Piper Cancer Institute (T.S.), Minneapolis, Minnesota.
Reprint requests: Timothy D. Sielaff, M.D., Ph.D., Virginia Piper Cancer Institute, Minneapolis, MN 55407. e-mail: timothy.sielaff@allina.com

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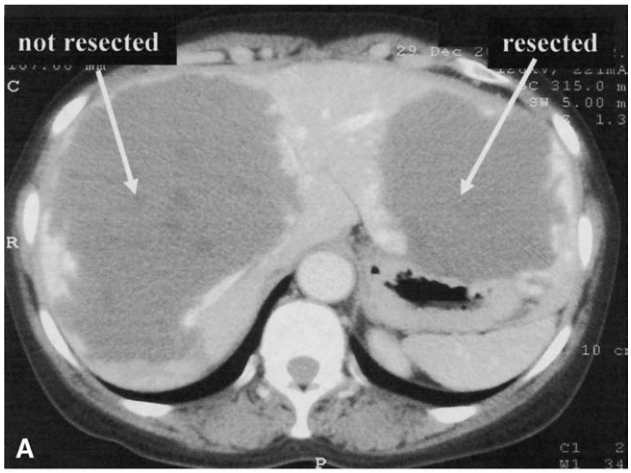
hemangiomas (Fig. 1, *A* and *B*). A segment III hemangioma was 9.5 cm in maximal diameter; a segment VI, VII, and VIII hemangioma was 12 × 16 cm; and an additional mass arising from segment IVB was about 14 × 19 cm.

Surgical resection of the symptomatic hemangiomas in segments III and IVB was recommended. The hemangioma in the right lobe of the liver was not symptomatic and was not amenable to safe anatomic resection because of right and middle hepatic vein involvement. Both lesions (Fig. 2, *A* and *B*) were enucleated at operation. The estimated blood loss was 400 mL. Two units of crossmatched packed red blood cells (RBCs) was transfused in the recovery room for hemoglobin of 7.3 mg/dL. Both units of the transfused cells were negative for the M red cell antigen, because the patient's preoperative indirect antiglobulin screening results had been positive for anti-M antibodies.



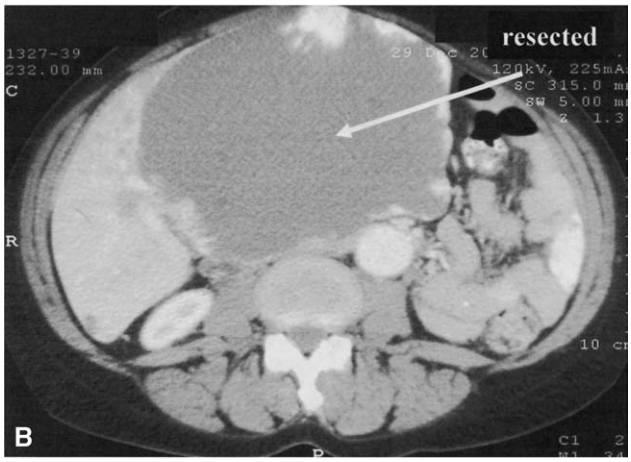


Fig. 1. Helical computed tomography scan showing (**A**) two hemangiomas measuring 9.5 cm in segment III (resected) and a 12 × 16-cm hemangioma derived from segments VI, VII, and VIII (not resected) and (**B**) the other 14 × 19-cm mass in segment IVB (resected).

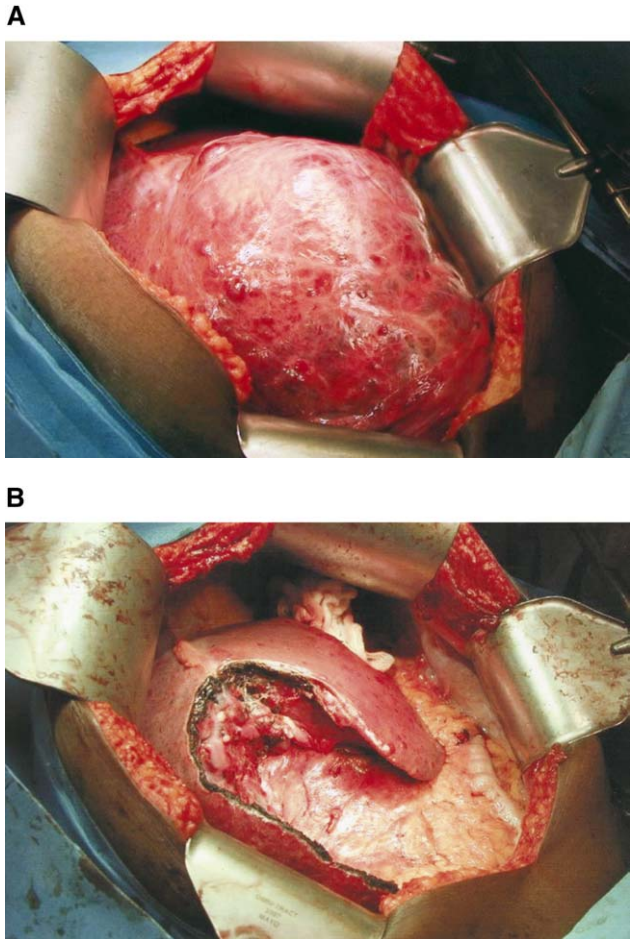


Fig. 2. Intraoperative photographs showing (**A**) the giant segment IVB hemangioma upon opening the abdomen and (**B**) the hepatic defect created after resection.

The remainder of her initial postoperative course was uneventful. Her hemoglobin concentration was followed closely during her 5-day hospital course and stabilized at 8.0 g/dL for the remainder of her hospitalization. She remained asymptomatic and so did not receive additional units of blood. She was discharged to home on postoperative day 5. At the time of her discharge, her total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, serum creatinine, and INR values were all within normal limits. Her discharge medications included her prior antihypertensive drugs with the addition of oxycodone, acetaminophen, bisacodyl, docusate, and ferrous sulfate. Pathologic examination of the tumors confirmed benign giant hemangiomas.

On postoperative day 12, the patient returned to the hospital with a several-day history of lethargy,

malaise, and nausea. She had also noticed her urine turning dark red for the first time, 2 days earlier. She had not taken any new medications except the ones prescribed on discharge 1 week earlier. Her vital signs were normal. Physical examination was remarkable only for conjunctival pallor and jaundice. The liver was palpable at 4 cm below the costal margin but was nontender. We noted no splenomegaly. The surgical incision was healing well without signs of infection. A Doppler ultrasound of the liver confirmed the patency and antegrade flow in the portal vein, hepatic artery, and left hepatic vein. A contrast-enhanced CT scan demonstrated no intra-abdominal fluid collections.

Laboratory test results were remarkable for a hemoglobin concentration of 6.6 g/dL, a hematocrit of 22.3%, a mean corpuscular volume of 80 fL, a red cell distribution width of 16.5%, a platelet count of 326×10^9 per liter, an RBC count of 2.14×10^{12} per liter, and a white blood cell (WBC) count of 9.8×10^9 per liter. The differential on the WBC count was 71% neutrophils and 19% lymphocytes. Her AST was 68 U/L, total bilirubin 5.6 mg/dL (unconjugated fraction, 4.8 mg/dL), blood urea nitrogen (BUN) 33 mg/dL, and creatinine 2.9 mg/dL. Other liver function test results and total creatinine kinase (CK) levels were normal.

The urine appeared frothy and dark red. Urinalysis revealed cloudy, brown urine with a specific gravity of 1.010, a large amount of blood detected, protein albumin of 100 mg/dL, and a urobilinogen level of 0.2 Ehrlich Unit dL. Urine microscopy revealed 25 WBCs per high-power field but was negative for RBCs. The fractional excretion of sodium was 1.7% with a urinary creatinine of 88 mg/dL and urinary sodium of 69 mmol L. The activated partial thromboplastin time (aPTT), INR, and serum fibrinogen levels were normal. Urine hemoglobin and hemosiderin values were both positive, as was the serum free-hemoglobin value.

The plasma hemoglobin level was 218 mg/dL (normal range, 0–15 mg/dL). In addition, the serum haptoglobin level was undetectable, and the serum lactate dehydrogenase (LDH) value was markedly elevated at 3300 U/L. The peripheral blood smear (Fig. 3) showed marked normochromic normocytic anemia, with occasional echinocytes and schistocytes; the increased polychromasia was consistent with a mild microangiopathic hemolysis. The reticulocyte count was 3.5%. An indirect antiglobulin test was again positive for alloantibodies against the red cell antigen M. However, a direct antiglobulin test was negative for autoantibodies. The cold agglutinins and serum cryoglobulin test results were both negative.

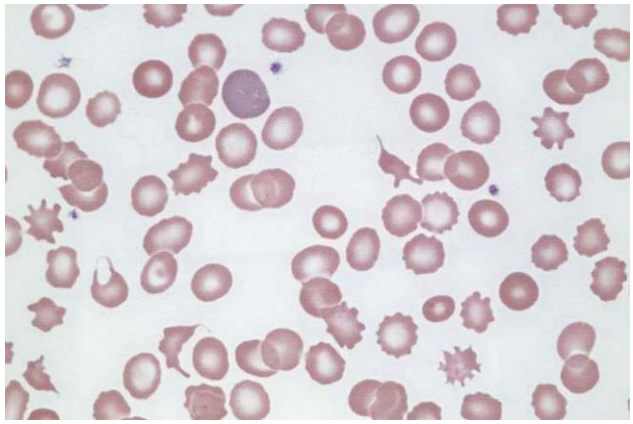


Fig. 3. Peripheral smear showing a small number of schistocytes with increased polychromasia, consistent with microangiopathic hemolytic anemia.

The patient was readmitted to the hospital and hydrated. Given her symptomatic anemia, she received 4 units of M-antigen–negative blood packed RBCs. The clinical picture was inconsistent with thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS); hence plasma exchange was not initiated. Within 3 days of readmission, the patient's discolored urine started to improve. It was completely clear by hospital day 5. After her four transfusions, the patient's hemoglobin concentration remained stable at 9–10 g/dL with no need for further blood transfusion. With rehydration, her serum creatinine level also improved (from 2.6 to a nadir of 1.6 mg/dL). Her serum LDH level fell from 3300 to a normal 664 U/dL. She was discharged to home on hospital day 7 and has had a complete recovery 4 months later with normalization of both her hemoglobin and serum creatinine levels.

Further testing with flow cytometry revealed a small subpopulation of white cells (3%); on staining, the glycosylphosphatidylinositol-liganded antigens CD55 and CD59 showed diminished intensity, suggesting enhanced susceptibility to lysis by complement activation. However, repeat testing 4 weeks after she had been readmitted revealed normal subpopulation characteristics, indicating that complement activation was not the initiating cause of her hemolysis. The 2 units of packed RBCs the patient had received postoperatively during her first hospitalization were rechecked: both were M-antigen negative. Results of repeated direct antiglobulin testing were negative for both complement and IgG. Results of a Heinz body preparation test were negative, and the patient's glucose 6-phosphate dehydrogenase (G6PD) level was normal. A summary of the tests performed to confirm our diagnosis of MAHA are presented in Table 1.

Table 1. Tests for postoperative nonhemorrhagic anemia

System	Test	Purpose	Result	Interpretation	Diagnosis
Renal	Creatinine	Evaluate renal function	2.9 mg/dL	Decreased function	Acute renal failure
	BUN	Evaluate renal function	33 mg/dL	Decreased function	Acute renal failure
	Urobiliniogen	Evaluate bilirubin in urine	Positive	Excess bilirubin in serum	Hyperbilirubinemia
	Microscopic urinalysis	Evaluate tubule damage, glomerular damage	Few RBCs, many WBCs	Positive hemoglobin on dipstick not from RBCs	Renal tubular damage and hemolysis
	Hemosiderin	Made by kidney to bind to free hemoglobin	Positive	Overwhelming intravenous hemolysis	Intravascular hemolysis with renal damage, possible PNH
Hepatic	ALT, AST	Evaluate hepatocellular damage	Normal	Normal hepatocyte function	No liver failure
	Bilirubin (total and unconjugated)	Decreased clearance or increased production	5.6 and 4.8 mg/dL	Likely increased Production	Normal liver function with increased production of bilirubin
	LDH	Not liver specific, evaluate large-scale cell death	3,300 U/L	Large-scale cell death present	Supports hemolysis
	INR, aPTT	Coagulation ability, component production by liver	Normal	Normal coagulation	Anemia not likely result of coagulation deficiency
Hematologic	Hemoglobin	Evaluate circulating concentration	6.6 g/dL	Low and expected decreased oxygen-carrying capacity	Hemoglobinemia
	Platelet count	Count circulating platelets	326×10^9/L	Normal, not consumed, sequestered, or destroyed	Not Kasabach-Merritt, TTP, DIC, HUS
	Fibrinogen	Evaluate degree of intravascular thrombus formation	Normal	Not being consumed	Not DIC
	Free hemoglobin	Degree of hemolysis	218 mg/dL	Severe hemolysis	Could be Kasabach-Merritt, HUS, TTP, MAHA, DIC
	Haptoglobin	Binds free hemoglobulin	Undetectable	Consumed when bound	Severe hemolytic anemia
	G6PD	Enzyme for Pentose shunt, NADP reduction	Normal	No enzyme deficiency leading to shortened RBC life span	Not cause of hemolysis
	Peripheral smear	Evaluate for morphologic changes	Normocytic/chromic, schistocytes present	Fragmented and damaged RBCs	Not folate, B_{12}, or iron deficiency, MAHA
	Heinz body preparation	Precipitated hemoglobin		Inefficient clearance by spleen	Severe intravenous hemolysis

(Continued)

Table 1. Continued

System	Test	Purpose	Result	Interpretation	Diagnosis
Immunologic	Cryoglobulin	Antibody associated with disease hemolysis	Normal	No hemolysis associated with antibodies and acute disease	No acute antibody associated hemolysis
	Flow cytometry for CD 55, 59	RBC surface proteins that inhibit abnormal complement activation	Normal	Not genetically predisposed to complement-mediated hemolysis	Not PNH
	Cold agglutinins	Antierythrocyte antibodies	Negative	Hemolysis not caused by cold agglutinins	Not cold agglutinin disease
	Direct antiglobulin	Tests for autoantibodies to RBCs	Negative	No antibodies or complement on own RBCs	Not autoimmune hemolytic anemia
	Indirect antiglobulin	Tests for alloantibodies and autoantibodies to donor RBCs	Positive M-antibody	Cross-matched blood retested and OK	Not delayed transfusion reaction, not PNH

See text for abbreviations.

DISCUSSION

This patient's acute MAHA and renal insufficiency were clearly related to the major surgical procedure performed. It is hypothesized that a transient alteration in the blood flow within the remaining hemangioma, after resection of the other 2, led to endothelial injury. This injury mediated complement activation, resulting in local thrombosis with platelet aggregation and, by means of the change in vascular diameter and dimensions, mechanical destruction of red cells (per the classic mechanism as described by Brain[18]). He hypothesized that the endothelium inside the hemangiomas is susceptible to damage induced by changes in flow, pressure, and thrombus formation, resulting in increased shear forces. These changes in external forces on the erythrocyte may result in hemolysis and further damage to the endothelium, which can then lead to initiation of the coagulation cascade resulting in consumptive coagulopathy and DIC. Surgeons should be aware of this potential systemic complication and its systematic evaluation and treatment when performing any major surgery in the setting of untreated giant hemangiomas.

A form of intravascular hemolysis, MAHA is characterized by fragmentation of red cells.[8] Typically, fragmentation is due to either endothelial injury (e.g., patients with systemic vasculitides, catastrophic antiphospholipid syndrome, preeclampsia of pregnancy, stem cell transplant, and TTP or HUS) or abnormal blood flow (e.g., in bypass patients or those with mechanical heart valves or intra-aortic balloon pumps).[9,11,23,24] MAHA in the setting of giant hemangiomas was first described by Brain in 1970[18]; it presumably resulted from a combination of abnormal blood flow and endothelial injury. His report was followed by several others—Prematilleke[20] in 1972, Hagerman et al.[15] in 1975, Linderkamp et al.[21] in 1976, Watanabe et al.[11] in 1978, Maeda et al.[17] in 1981, Shimizu et al.[14] in 1990, Yohannan et al.[12] in 1990, and Mazoyer et al.[25] in 2002). MAHA in the setting of arteriovenous malformations is often referred to as Kasabach-Merritt syndrome if accompanied by consumptive coagulopathy with hypofibrinogenemia, elevated fibrin degradation products, and thrombocytopenia.[17,18,25] DIC has previously been reported after incomplete resection of giant cavernous hemangiomas.[11,12,16,24] However, what all of the patients in previous reports had in common was consumptive coagulopathy with thrombocytopenia with or without hemolysis. Chronic intravascular hemolysis and consumptive coagulopathy are indications for surgery.[15,19,21,23] Until now, no authors had ever reported isolated MAHA *after* surgical resection.

The cause of our patient's postoperative acute intravascular hemolysis appears to have been mediated by the presence of the remaining giant hemangioma. The timing of hemolysis in relation to her postoperative blood transfusions and to her positive indirect antiglobulin screen for alloantibodies at first pointed to delayed transfusion reaction. However, both of the transfused RBC units were M red cell antigen negative and her hemolytic anemia was predominantly intravascular, so her delayed transfusion reaction was ruled out. Given the absence of thrombocytopenia, TTP and HUS were also ruled out. Similarly, paroxysmal nocturnal hemoglobinuria (PNH) and oxidant hemolysis, both of which could lead to acute hemolysis, were ruled out after appropriate testing.

Several authors have previously reported severe hematologic derangements associated with hemangiomas. Shimizu et al. reported similar hematologic findings in a patient, including the lack of thrombocytopenia (that differentiates MAHA from Kasabach-Merritt syndrome).[11,12,19] The authors presumed that the patient's consumptive coagulopathy was occurring in the tumor, as evidenced by the normalization of hematologic test results after tumor resection. Jona et al.[10] described a pediatric patient who had multiple congenital subcutaneous giant hemangiomas who underwent a series of resections over a period of years. After each resection (with one exception), the patient experienced severe postoperative bleeding and was diagnosed with DIC and MAHA. Others have described similar cases in which DIC and MAHA developed in a patient with subcutaneous hemangiomas after surgery was performed on distant organs.[23] Both authors concluded that the consumption and hemolysis were triggered by endothelial damage during resection resulting in thrombosis and platelet sequestration in the hemangiomas. This would lead to hemolysis secondary to the shear injury to the erythrocytes.

CONCLUSION

Our patient experienced a significant isolated MAHA and acute renal failure in the early postoperative period after surgical stress in the setting of an unresectable giant cavernous hemangioma. After ruling out any major vascular surgical complications, a systematic hemolysis evaluation must be performed and therapy initiated (Fig. 4). This therapy should include appropriate hydration, transfusion of deficient blood components appropriate to the type of anemia

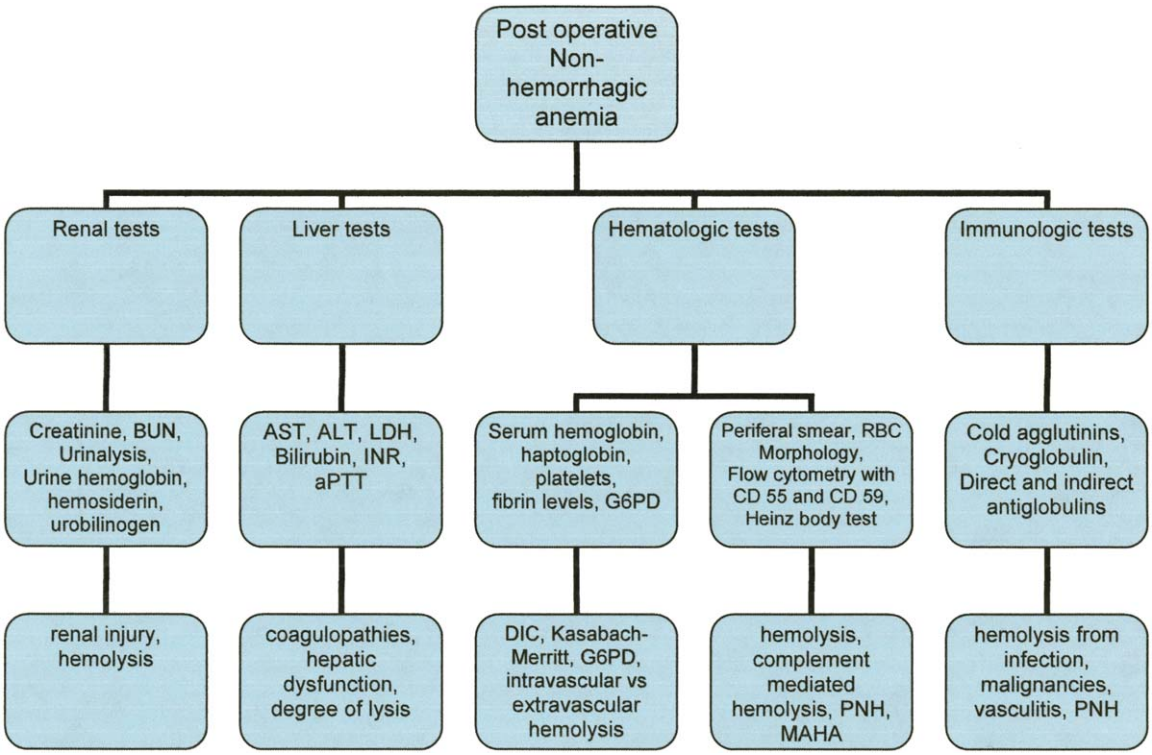


Fig. 4. Flowchart depicting a generalized workup for postoperative anemia that is not due to hemorrhage or technical complication. (See text for abbreviations.)

experienced, and early involvement of a medical hematologist for initiation of plasmaphoresis, dialysis, or component transfusion if necessary. MAHA and other coagulopathies must be considered as potential complications when major surgery is performed in patients with giant hemangiomas.

We are grateful for the expert editorial assistance of Dr. Mary E. Knatterud.

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Mirizzi Syndrome and Gallstone Ileus: An Unusual Presentation of Gallstone Disease

Marcelo A. Beltran, M.D., Attila Csendes, M.D., F.A.C.S.

We discuss the case of a man with an unusual complication of gallstone disease. An 85-year-old patient presented to the emergency department with a 3-week history of abdominal pain in the right upper abdominal quadrant. Thoracoabdominal radiography demonstrated that the whole extrahepatic biliary tree, including the common bile duct, common hepatic duct, gallbladder, and left and right hepatic ducts, were visibly delineated by air. The operative findings revealed a small shrunken gallbladder, a fistula between the gallbladder fundus and the gastric antrum, and a cholecystohepatic fistula, corresponding to Mirizzi syndrome, type II. A large gallstone was found impacted in the jejunum. This patient seems to have developed initially a cholecystohepatic fistula. Due to the acute inflammatory process, the stone eroded through the gallbladder wall and into the gastric antrum, passing from the antrum into the small bowel, where it became impacted. We suggest that the natural history of Mirizzi syndrome does not end with a cholecystobiliary fistula but that the continuous inflammation in the triangle of Calot may result in a complex fistula involving not only the biliary tract but also the adjacent viscera.
(J Gastrointest Surg 2005;9:686–689)

Key words: Mirizzi syndrome, gallstone ileus, complications

The most common complications of chronic gallstone disease are acute cholecystitis, acute pancreatitis, cholangitis, and a gangrenous gallbladder.[1] Other complications are extremely rare and include Mirizzi syndrome, cholecystocholedochal fistula, and gallstone ileus.[1–10] The late nineteenth century and early twentieth century surgical literature are rich in descriptions of bizarre complications of long-standing gallstone disease.[11–20] Those complications are seldom found today. The current knowledge of biliary disease and the widespread use of ultrasonography have led to early diagnosis and early treatment for those with gallstone disease. Usually patients with gallstone disease have only the most common complications associated with their disease.

External compression of the biliary tree resulting in obstructive jaundice was described by Kehr[13] in 1905, Ruge[14] in 1908, Levrat and Chayvialle in 1941[15], and Mirizzi[17] in 1948. Puestow[16] first described a cholecystobiliary fistula in 1942; Behrend and Cullen[18] in 1950 and Mirizzi[19] in 1952 reported other cases. Courvoisier[11] initially described so-called gallstone ileus resulting from obstruction of the small bowel by an impacted gallstone in 1890. In 1896, Bouveret[12] described a syndrome of gastric outlet obstruction caused by an impacted gallstone in the duodenal bulb after the migration of the stone through a cholecystoenteric fistula.

Until the early 1980s, these cases were considered as separate entities. The diagnosis and surgical approach were almost anecdotal.[4,5] In 1982 McSherry et al.[2] and Csendes et al.[3] in 1989 published seminal articles describing the physiopathologic process and classifying Mirizzi syndrome. These articles formed the basis on which the surgical approach to the Mirizzi syndrome was standardized.[3,6,7,9] We report herein an older patient who had both Mirizzi syndrome and gallstone ileus.

CASE REPORT

An 85-year-old man presented to the emergency department with a 3-week history of right upper abdominal quadrant pain. He was anxious and had shortness of breath. The pain was associated with nausea and protracted vomiting that had debilitated

From the Department of Surgery (M.A.B.), Emergency Unit, Hospital de Ovalle, Ovalle, Chile; and Department of Surgery (A.C.), Clinical Hospital, Universidad de Chile, Santiago, Chile.
Reprint requests: Marcelo A. Beltran, M.D., Plazuela Baquedano 240, Ovalle, IV Region, Chile. e-mail: beltran_01@yahoo.com

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him. He could not eat, and he was very weak. The physical examination revealed a malnourished pale man who was febrile, sweating, and delirious. The arterial pressure was stable but he had a rapid pulse. The abdomen was tender, principally in the upper right and left quadrants, and he had rebound sensitivity. The laboratory examinations revealed a hemoglobin of 12.2 g/dl, a white blood cell count of 13.6×10^9/L, a total bilirrubin of 0.69 mg/dl, and a direct bilirubin of 0.07 mg/dl. The alkaline phosphatase level was 103 U/L.

Plain radiographs of the thorax, abdomen, and pelvis were obtained, along with an abdominal ultrasound. The thoracoabdominal radiograph demonstrated a curious finding. The entire extrahepatic biliary tree, including the common bile duct, the common hepatic duct, the gallbladder, the left and right hepatic ducts, and some of the smaller intrahepatic radicals, were clearly visible, delineated by air. The gastric antrum was also visible (Fig. 1). This unusual finding was interpreted as a biliodigestive fistula. A water-soluble contrast radiograph was subsequently taken, and it demonstrated a large gallstone lodged 60 cm distal to the ligament of Treitz (Fig. 2).

About 24 hours later, the patient underwent surgery. The operative findings were a small shrunken gallbladder, a fistula between the gastric antrum and the gallbladder fundus, and a cholecystohepatic fistula corresponding to Mirizzi syndrome type II, as described by Csendes et al.[3] A large gallstone, 45 mm in diameter, was found in the jejunum, impacted 60 cm from the ligament of Treitz. The stone was milked proximally into a dilated healthy area and retrieved via a longitudinal enterotomy.

The biliodigestive fistula was divided, and the opening was closed with a 4-0 polyglycolic acid suture. The cholecystohepatic fistula was sutured over a cuff of gallbladder with the same material. A T tube was placed into the common bile duct, and an intraoperative cholangiograph was taken. Two drains were left in place, and a nasojejunal tube was inserted for postoperative feeding.

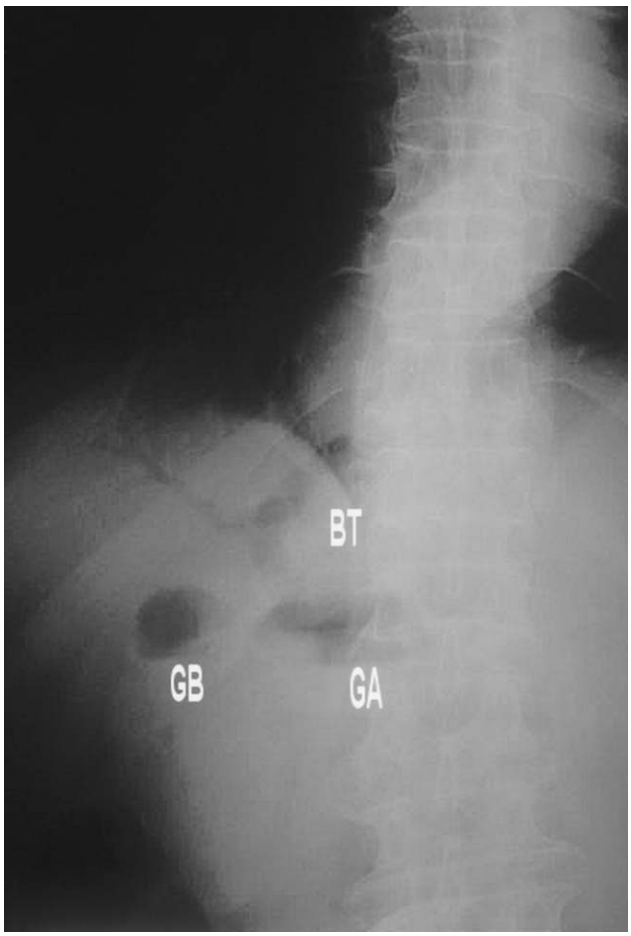

Fig. 1. The complete biliary tract is clearly delineated by air, including the gallbladder (GB), the common, right, and left hepatic ducts, the common bile duct (BT), and some intrahepatic radicals. The gastric antrum (GA) also contains air.

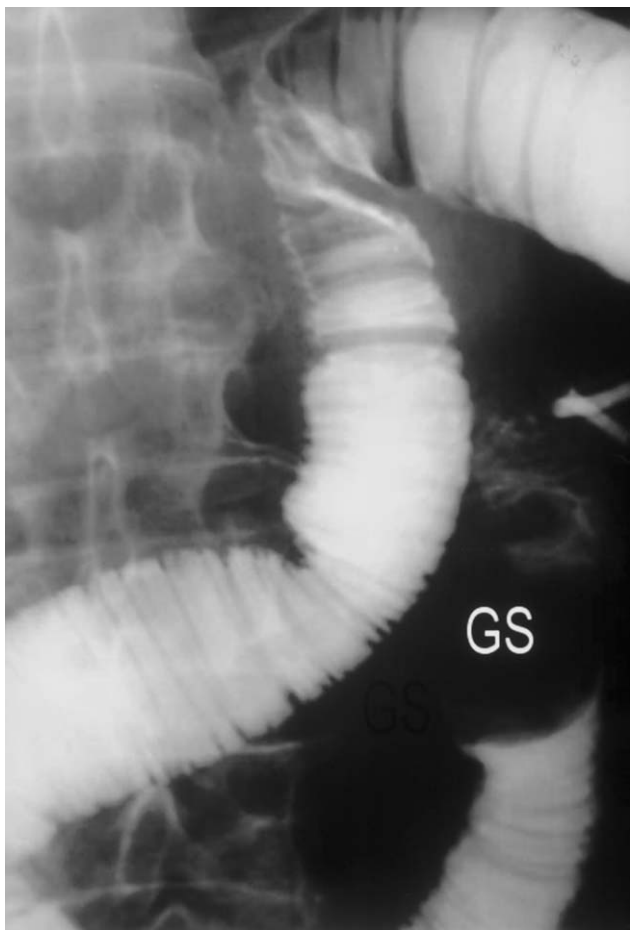

Fig. 2. Water-soluble contrast radiography showing the outline of a large gallstone (GS) impacted in the jejunum.

The postoperative course was uneventful, and the patient recovered. He was discharged on postoperative day 7, on oral feeding, and without drainage from his abdominal drains. A postoperative cholangiograph through the T tube demonstrated only a dilated bile duct, no stones or other anomalies. The T tube was removed 60 days after the operation.

DISCUSSION

The original description by Puestow[16] in 1942 of a cholecystobiliary fistula and the report of Mirizzi[17] in 1948 of a functional obstructive syndrome, both as complications of longstanding gallstone disease, led some surgical investigators to relate the two processes.[2,3] The physiopathologic process was elucidated after almost 40 years, in part due to the relative difficulty in the diagnosis that it represents[1–9] and to the low incidence reported.[2,3,6–9]

As stated by Csendes et al.,[3] the so-called Mirizzi syndrome and the cholecystobiliary fistula are different evolving stages of the same disease process. The concepts that an impacted stone in close contact with an inflamed mucosa develops first ischemia and then necrosis and that, because of the associated inflammation of the gallbladder wall and the hepatic or common bile duct wall, the impacted stone erodes through them and eventually forms a fistula are applicable to other biliary fistulas, such as cholecystoduodenal, cholecystogastric, and cholecystocolonic fistulas.[3,6–10]

This particular patient seems to have developed initially a cholecystohepatic fistula. After the last 3 weeks of his disease, due to the acute inflammatory process, the large stone found in the jejunum eroded through the gastric antrum wall, passing into the small bowel, where it became impacted. That could be the reason why we found this complex fistula, which appeared on the thoracoabdominal roentgenogram (Fig. 1).

The classic radiographic signs of gallstone ileus were first described by Rigler[21] in 1941 and included signs of intestinal obstruction, pneumobilia, aberrantly located gallstone, and change in location of the previously identified stone on serial examinations. Our patient presented with pneumobilia as well as two adjacent air-fluid levels in the right upper quadrant. This sign, as described by Balthazar[22] in 1978, is an additional helpful sign. The medial collection is located in the duodenal bulb and the lateral in the gallbladder (Fig. 1). It should be noted that even though the stone was large, it did not become impacted at the pylorus, so this patient did not develop Bouveret syndrome.[10,12] Instead the stone migrated through the pylorus, the duodenum, and the first 60 cm of the jejunum until it became impacted (Fig. 2), causing the characteristic syndrome of intestinal obstruction known as gallstone ileus.

CONCLUSION

We may consider the torpid evolution of this patient's complication as a lesson in advanced biliary pathology. We also suggest that the natural history of Mirizzi syndrome may not end with just a cholecystobiliary fistula. The continuous inflammation in the triangle of Calot area may result in a complex fistula involving not only the biliary tract but also the adjacent viscera.

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Computed Tomography Diagnosis of Ischemia and Complete Obstruction in Small Bowel Obstruction: A Systematic Review

Rebecca D. Mallo, B.S., Leon Salem, M.D., Tasneem Lalani, M.D., David R. Flum, M.D., M.P.H.

This review was designed to describe the diagnostic performance of computed tomography (CT) in assessing bowel ischemia and complete obstruction in small bowel obstruction (SBO). A MEDLINE search (1966–2004) identified 15 studies dealing with the CT diagnosis of ischemia and complete obstruction in SBO. Ischemia was defined by operative findings, and complete obstruction was defined by enteroclysis or operative findings. Aggregated sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated. Eleven of 15 studies reported on the CT diagnosis of ischemia in SBO based on 743 patients. The aggregated performance characteristics of CT for ischemia in SBO were sensitivity of 83% (range, 63–100%), specificity of 92% (range, 61–100%), PPV of 79% (range, 69–100%), and NPV of 93% (range, 33.3–100%). Seven of 15 studies evaluated the CT classification of complete obstruction based on 408 patients. The aggregated performance characteristics of CT for complete obstruction were sensitivity of 92% (range, 81–100%), specificity of 93% (range, 68–100%), PPV of 91% (range, 84–100%), and NPV of 93% (range, 76–100%). This review demonstrates the high sensitivity of CT for ischemia in the setting of SBO and suggests that a CT scan finding of partial SBO is likely to reflect a clinical condition that will resolve without surgical intervention. (J GASTROINTEST SURG 2005;9:690–694)

KEY WORDS: Bowel obstruction, computed tomography, sensitivity and specificity, ischemia/diagnosis

In the management of small bowel obstruction (SBO), patients with ischemia or irreversible obstructions need to be differentiated from those with reversible, non-threatening conditions. Patients with ischemia require urgent intervention or can progress to bowel necrosis, sepsis, and death. Early detection of patients with SBO and ischemia should improve the outcomes of these sequelae. Another group of patients who benefit from earlier operative intervention include those without ischemia but who have a condition that will not reverse without surgical intervention. Identifying patients with irreversible SBO might direct them to definitive therapy without unnecessary use of resources and delay until definitive therapy.

The diagnosis of ischemic bowel in SBO using clinical evaluation, laboratory testing, and plain radiography is not reliable.[1] Similarly, plain radiography is not accurate in diagnosing the irreversibility of SBO.[2] A complete or high-grade SBO is considered by many surgeons to describe a condition that will not resolve without operative intervention.[3,4] The purpose of this study was to systematically review the diagnostic accuracy of CT for ischemia and complete obstructions in patients with SBO to help better assess its role in the management of these patients.

MATERIALS AND METHODS

A systematic and comprehensive review of the scientific literature was conducted using MEDLINE and Cochrane databases for the period 1966–2004. This reproducible search identified all publications related to CT evaluation of patients with SBO.

From the Departments of Surgery (R.D.M., L.S., D.R.F.), Radiology (T.L.), and Health Services (D.R.F.), University of Washington, Seattle, Washington.
Reprint requests: David R. Flum, M.D., M.P.H., University of Washington, Department of Surgery, BB 431, 1959 NE Pacific Street, Box 356410, Seattle, WA 98195-6410. e-mail: daveflum@u.washington.edu

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Search Strategy/Inclusion Criteria

Two combined search strategies were used: (1) ("intestinal obstruction/radiography" [MeSH] AND "Intestine, Small" [MeSH] AND "Tomography, X-ray Computed" [MeSH] and (2) ("CT" OR "computed tomography") AND "small bowel obstruction"). Studies with primary data collection on patients who presented with clinical signs and symptoms of SBO and subsequently underwent CT scanning were included. The report needed to establish whether the SBO was classified as complete or high-grade, or if ischemia was identified on CT.

Exclusion Criteria

The search was limited to studies involving human subjects published in the English language. Case reports, abstracts only, letters, incomplete reports in surveys, and reviews were excluded. Studies in which the degree of obstruction was not reported were also excluded.

Search Yield

Using the inclusion criteria, 291 publications were detected. Seventy-three publications did not contain data relevant to the research study. Two hundred three met the exclusion criteria of case reports, abstracts, letters, and incomplete reports in surveys and reviews and therefore were excluded. Fifteen articles were reviewed, and citations from these reports were used to identify additional studies but no further studies were found.

Analysis

Two aggregated datasets were constructed—the first including studies that reported the CT diagnosis of bowel ischemia in SBO and the second set including studies that reported the CT diagnosis of complete or high-grade SBO. Results for the diagnosis of complete and high-grade SBO were aggregated together because both of these are generally considered to necessitate surgical treatment.[3,4] Two of the studies were used in both sets because they included data on both the presence of complete or high-grade obstruction and the presence of ischemia or strangulation. For each dataset, the PPV, NPV, sensitivity, and specificity were calculated for CT in detecting intestinal ischemia or complete/high-grade obstruction. The standard of reference for small bowel ischemia was a finding of ischemia at the time of operation (for the patients who were operated) or a discharge diagnosis of SBO without ischemia (for the patients who were not operated). The standard of reference for complete/high-grade obstruction was either a finding of complete SBO at the time of operation (five studies) or enteroclysis (two studies). Patients who were reported to have any other cause of intestinal ischemia (e.g., mesenteric infarction) were excluded from this analysis.

RESULTS

Ischemia/Strangulation

Eleven studies reported on the CT diagnosis of ischemia in SBO and included 743 patients (Table 1). The aggregated diagnostic values of CT for bowel ischemia in SBO were PPV of 79% (167 of 212; range, 69–100%), NPV of 93% (496 of 531; range, 33.3–100%), sensitivity of 83% (167 of 202; range, 63–100%), and specificity of 92% (496 of 541; range, 61–100%).

Complete/High Grade

Seven studies evaluated the accuracy of CT in detecting the grade of obstruction, classified as complete/high-grade or partial SBO, and included 408 patients (Table 2). The aggregated diagnostic values of CT for high-grade/complete obstruction were PPV of 92% (168 of 182; range, 84–100%), NPV of 93% (211 of 226; range, 76–100%), sensitivity of 92% (168 of 183; range, 81–100%), and specificity of 94% (211 of 225; range, 68–100%).

DISCUSSION

In this systematic review, we found that CT is a highly accurate modality for diagnosing ischemic bowel in patients with a sensitivity of 83%, specificity of 92%, PPV of 79%, and NPV of 93%. Although other diagnostic modalities for ischemia in the setting of SBO might detect only 50% of cases,[1] these performance characteristics of CT indicate that 83% of cases would be identified and that if no ischemia was identified by CT then there was a 92% chance that no ischemia is present. The diagnostic accuracy of CT was also good for complete/high-grade SBO, with aggregated sensitivity, specificity, PPV and NPV over 90%, but metrics of diagnostic performance for complete SBO are more problematic because of the lack of a "gold standard" for complete SBO. The PPV and NPV for ischemia are reliable based on discrete surgical findings or resolution without operation. Because ischemia is unlikely to resolve without surgery,[3] resolution without operation suggests that ischemia was not present and therefore CT scan appears to be an important modality in detecting ischemia. Conversely, the decision to operate on patients

Table 1. Studies reporting computed tomography diagnosis of bowel ischemia in small bowel obstruction

Study	Study Design	Diagnostic Performance
Balthazar et al., 1992[11]	Retrospective (n = 19)	PPV = 10/10 = 100% NPV = 3/9 = 33.3% Sens = 10/16 = 63% Spec = 3/3 = 100%
Balthazar et al., 1997[14]	Prospective (n = 98)	PPV = 19/24 = 79% NPV = 70/74 = 95% Sens = 19/23 = 83% Spec = 70/74 = 93%
Donckier et al., 1998[15]	Prospective (n = 54)	PPV = 16/19 = 84% NPV = 35/35 = 100% Sens = 16/16 = 100% Spec = 35/38 = 92%
Frager et al., 1996[13]	Prospective (n = 60)	PPV = 29/41 = 71% NPV = 19/19 = 100% Sens = 29/29 = 100% Spec = 19/31 = 61%
Frager et al., 1995[22]	Prospective (n = 36)	PPV = 4/4 = 100% NPV = 32/32 = 100% Sens = 4/4 = 100% Spec = 32/32 = 100%
Kim et al., 2004[27]	Retrospective (n = 136)	PPV = 47/59 = 80% NPV = 58/77 = 75% Sens = 47/66 = 71% Spec = 58/70 = 83%
Makanjuola, 1998[25]	Retrospective (n = 49)	PPV = 2/2 = 100% NPV = 46/47 = 98% Sens = 2/3 = 67% Spec = 46/46 = 100%
Obuz et al., 2003[28]	Prospective (n = 41)	PPV = 6/6 = 100% NPV = 35/35 = 100% Sens = 6/6 = 100% Spec = 35/35 = 100%
Peck et al., 1999[26]	Retrospective (n = 55)	PPV = 3/3 = 100% NPV = 51/52 = 98% Sens = 3/4 = 75% Spec = 51/51 = 100%
Taourel et al., 1995[29]	Prospective (n = 52)	PPV = 9/13 = 69% NPV = 36/39 = 92% Sens = 9/12 = 75% Spec = 36/40 = 90%
Zalcman et al., 2000[30]	Prospective (n = 143)	PPV = 22/31 = 71% NPV = 111/112 = 99% Sens = 22/23 = 96% Spec = 111/120 = 93%

PPV = positive predictive value, NPV = negative predictive value, Sens = sensitivity, Spec = specificity.

Table 2. Studies reporting computed tomography diagnosis of complete/high-grade small bowel obstruction

Name	Study Design	Diagnostic Performance
Frager et al., 1995[22]	Prospective (n = 36)	PPV = 16/16 = 100% NPV = 20/20 = 100% Sens = 16/16 = 100% Spec = 20/20 = 100%
Frager et al., 1994[23]	Prospective (n = 90)	PPV = 46/50 = 92% NPV = 40/40 = 100% Sens = 46/46 = 100% Spec = 40/44 = 91%
Daneshmand et al., 1999[24]	Retrospective (n = 45)	PPV = 13/14 = 93% NPV = 30/31 = 97% Sens = 13/14 = 93% Spec = 30/31 = 94%
Maglinte et al., 1996[2]	Retrospective (n = 78)	PPV = 23/26 = 88% NPV = 47/52 = 90% Sens = 23/28 = 82% Spec = 47/50 = 94%
Maglinte et al., 1993[21]	Retrospective (n = 55)	PPV = 17/17 = 100% NPV = 34/38 = 89% Sens = 17/21 = 81% Spec = 34/34 = 100%
Makanjuola, 1998[25]	Retrospective (n = 49)	PPV = 21/21 = 100% NPV = 27/28 = 96% Sens = 21/22 = 95% Spec = 27/27 = 100%
Peck et al., 1999[26]	Retrospective (n = 55)	PPV = 32/38 = 84% NPV = 13/17 = 76% Sens = 32/36 = 89% Spec = 13/19 = 68%

with a "complete" SBO may have been influenced by the CT and therefore was not necessarily a reflection of underlying pathology. The NPV is probably the most reliable metric for evaluating CT scans of complete SBO because it is based on the cases that were not considered complete but instead resolved without surgery. The importance of this finding is that in patients without CT scan findings of complete SBO (partial SBO), resolution without surgery was noted in more than 90%.

Early detection of bowel ischemia in SBO is critical because it mandates an operation,[3–5] as ischemia is associated with an increased death rate.[6] The management of SBO is challenging because clinical, laboratory, and plain radiographic evaluations cannot reliably establish or exclude the diagnosis of bowel ischemia.[7,8] In a prospective trial of 51 consecutive patients who were about to undergo laparotomy for complete SBO,[1] the accuracy of both preoperative testing and the clinical judgment of senior surgeons was evaluated in the diagnosis of intestinal ischemia. No preoperative clinical parameter proved to be highly sensitive, specific, or predictive of ischemia. Moreover, the senior surgeon's clinical judgment correctly predicted ischemia in only 48% of the patients.

Others have suggested that high preoperative levels of interleukin 6 are associated with intestinal ischemia, but the use of this laboratory test is not widespread.[9,10] CT has been proposed as a more reliable test to detect ischemia in the presence of SBO,[11–15] but its role in the management of patients with suspected SBO has not been established. In this study, although we found that CT had a high sensitivity for ischemic bowel, we found few standard criteria for diagnosis of ischemic bowel in SBO. Some suggest that a combination of signs may increase the diagnostic accuracy,[12,16] and an aggregate scoring system may be attractive.

CT was also found to have a high diagnostic accuracy for complete SBO if considering the performance of an exploratory laparotomy as a demonstration of a need for operation. This may not be a helpful designation if the goal is determining the role of CT scanning in SBO. The standard of reference for complete SBO in these studies was either surgery or enteroclysis, and patients who resolved without surgery were assumed to have partial SBO. This assumes that complete SBO is an irreversible process and, as such, mandates surgical intervention. However, the clinical significance of complete SBO is not completely understood, and complete SBO has been reported to resolve with nonoperative management in 25–65% of cases.[5,17–19] The dictum "never let the sun rise and set on an obstructed bowel" may be in evolution, and when looking at the trends over time, there has been a gradual increase in the delay to operation without an increase in the rate of mortality.[20] Furthermore, similar rates of bowel ischemia have been reported in patients with complete and partial SBO.[5] This study does shed some light on the predictive qualities of a CT designation of complete SBO. This aggregated analysis demonstrated that CT has an NPV of greater than 90% for complete SBO. Because these patients without complete SBO resolved with nonoperative management, we conclude that those without a complete SBO on CT have a 90% chance of resolving without surgery.

This review has several limitations. Studies included in our review varied in design, inclusion and exclusion criteria, CT scanning technique (helical versus sequential), use of contrast media, radiologic criteria used to diagnose ischemia and complete SBO, blinding of the radiologists to the clinical data, and the time of follow-up for those patients who did not undergo surgery. Given the variability in these studies and because none included prospective, randomized data, we believed that meta-analytic or higher-level statistical comparisons were inappropriate and have simply provided aggregated proportions. Although all studies used operative findings as their standard of reference for ischemia, the timing between CT scanning and surgery varied between studies and within the studies themselves. This issue may have influenced the results of the studies as SBO findings during the course of illness can change over time. These variations may have contributed to the wide range of reported performance of CT. Most important, the standard of reference to diagnose complete/high-grade SBO was enteroclysis in two studies,[2,21] whereas the others used surgery as their standard of reference.[22–26] Furthermore, two studies[2,23] did not specify if a false-positive result for bowel obstruction was partial or complete/high-grade SBO. To avoid overestimation of the diagnostic accuracy of CT in complete/high-grade obstruction, we assumed that a false-positive result was assigned to patients who did not have obstruction but were diagnosed as having complete/high-grade obstruction. In addition, although CT scan interpretations for SBO are often indeterminate, most of the studies reviewed have not addressed this issue. In one study,[24] there were five patients with indeterminate findings who were excluded from the study, and in another study,[21] a voting system was used for decision making in indeterminate cases. Other issues, including study cost, utilization of resources, management of false-positive values, and the optimal timing of CT scanning, were not included in this study and should be balanced against the accuracy of CT scanning in the relatively uncommon entity of bowel ischemia.

Although it is attractive to develop clinical protocols for the use of CT in the management of patients with SBO, the results of this review limit our ability to do so. Even though this review suggests that CT is quite accurate for ischemia, due to the heterogeneity of the CT scanning protocols (e.g., the use of contrast media, helical versus nonhelical CT), and heterogeneity of study populations (complete and partial SBO), definitive recommendations must be limited. Development of a clinical protocol would require evidence-based appraisal of the usefulness of CT scanning in patients with SBO as well as the cost-effectiveness of this technology. Both of these considerations are under review by our group.

CONCLUSION

In this review, we found that CT was highly accurate for the diagnosis of ischemia in SBO and, given the absence of other predictive variables for ischemia, these data suggest that the broader use of CT scanning may improve the management of SBO. The importance of CT scanning in diagnosing complete SBO is unclear given the heterogeneity of the definition and an inconsistent "gold standard." At least

90% of patients with a CT finding inconsistent with complete SBO resolve without operation. The clinical importance of the designation of complete SBO should be further evaluated prospectively to determine the true role of CT in the management of SBO.

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Adenocarcinoma After Ileoanal Anastomosis for Familial Adenomatous Polyposis: Review of Risk Factors and Current Surveillance Apropos of a Case

Fábio Guilherme Campos, M.D., Angelita Habr-Gama, M.D., Desidério Roberto Kiss, M.D., Edésio Vieira da Silva, M.D., Viviane Rawet, M.D., Antônio Rocco Imperiale, M.D., Rodrigo Perez, M.D., José Hyppólito da Silva, M.D., Afonso Henrique S. Sousa, Jr., M.D., Joaquim Gama-Rodrigues, M.D.

Restorative proctocolectomy has become the most common surgical option for familial adenomatous polyposis (FAP) patients, based on the premise that it provides good functional results and reduces colorectal cancer risk. But several adenomas may develop in the pouch mucosa over the years, and even cancer at the anastomosis or in the pouch mucosa has been reported rarely. This article aims to describe a case of pouch cancer after restorative proctocolectomy for FAP, reviewing the possible causes of this unfortunate outcome. A 40-year-old man started presenting with fecal blood loss 12 years after restorative proctocolectomy with mucosectomy and hand-sewn anastomosis for FAP. Proctologic examination revealed an elevated mass 3 cm from the anal margin, which biopsy determined to be a mucinous adenocarcinoma. The patient underwent pouch excision and terminal ileostomy. Histologic analysis showed a 2.2 cm mucinous adenocarcinoma between the ileal and anal mucosa (T2N0Mx) and multiple tubular microadenomas in the ileal pouch. The present case and the data presented here suggest that restorative proctocolectomy is not a "cancer-free" alternative to ileorectal anastomosis, because it does not remove the risk of metachronous intestinal neoplasia. Although the long-term risk of malignancy is not known, lifelong follow-up seems to be necessary after restorative proctocolectomy. Current recommendations for pouch surveillance are presented. (J GASTROINTEST SURG 2005;9:695–702)

KEY WORDS: Adenocarcinoma, ileal-pouch anal anastomosis, restorative proctocolectomy, familial adenomatous polyposis, cancer

INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomic hereditary disease characterized by the presence of numerous colorectal adenomatous polyps. It is associated with germinative or acquired mutations in the APC gene that predispose to cell proliferation and development of benign and malignant extracolonic manifestations in many organs.[1]

The disease may account for almost 1% of colorectal cancer (CRC) cases. The malignant evolution of colorectal polyps in the third to fourth decades of life is now practically an established, extensively documented fact, although the syndrome may present a variable biological and clinical behavior.[2] Thus, early detection, prophylactic colectomy, and family surveillance are the main steps in managing FAP patients. Furthermore, recognition and appropriate treatment of the associated extracolonic manifestations is essential to reduce disease morbidity.[3]

Surgical options include proctocolectomy and ileostomy, total abdominal colectomy with ileorectal anastomosis (IRA), and restorative proctocolectomy with an ileal pouch-anal anastomosis (RPC). Nowadays, permanent ileostomy is performed only in patients with advanced low rectal cancer or fecal incontinence.

In each patient, the surgical procedure should be selected on the basis of parameters such as age, site/number of the polyps, location of the mutation, and patient willingness to undergo regular check-ups.

From the Colorectal Surgery Division (F.G.C., A.H.-G., D.R.K., V.R., J.H.d.S., A.H.S.S.) and Department of Gastroenterology (E.V.d.S., A.R.I., R.P., J.G.-R.), Hospital das Clínicas—University of São Paulo School of Medicine, São Paulo, Brazil.
Reprint requests: Fábio Guilherme Campos, Alameda Jaú, 1477, Apt 111A, 01420-002, São Paulo (SP), Brazil. e-mail: fgmcampos@terra.com.br

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In this context, IRA and RPC are surgical procedures that yield different results in terms of functional capability and oncologic radicality. When selecting the primary surgery, one must remember that although IRA exhibits good surgical and functional outcomes,[4] it has been associated with an elevated risk of metachronous rectal cancer after IRA, with rates varying from 12% to 43%.[5,6]

Since its introduction to clinical practice, RPC has been progressively modified in an attempt to improve functionality and reduce complication rates while providing control of the mucosal disease.[7] Despite some controversies, many technical advances in pouch surgery have allowed it to become the gold standard for the elective treatment of ulcerative colitis (UC) and FAP patients.[8] In the latter, this technique aims to reduce CRC risk and maintain acceptable anal function,[9] although desmoid tumors and duodenal and ileal adenomas may still develop.[10]

RPC was initially thought to abolish the risk of colorectal adenoma development in FAP patients, making surveillance of the lower gastrointestinal tract no longer necessary. But several papers have documented the appearance of pouch adenomas after RPC, usually after an interval of several years.[11] The potential for adenomatous polyp formation in the terminal ileum has been estimated to manifest in 9% to 20% of FAP patients, even 25 years after the colectomy.[12]

Furthermore, rectal mucosa may be left behind after the stapled technique (with conservation of the anal transitional zone) or after the standard Park's procedure (because of incomplete mucosectomy), exposing the patient to the risk of polyp development and subsequent malignancy.

During the last decade, the description of some pouch cancer cases definitely confirmed that RPC is not a "cancer-free" alternative to IRA.[13–21] Subsequently, as the long-term risk of the development of malignancy after RPC has been evaluated, suggestions for surveillance have been recently raised in the literature.

The present paper describes a rare case of pouch cancer after RPC for FAP, reviews the cases published in the English literature, and discusses the potential carcinogenic mechanisms that may be involved in this outcome.

CASE REPORT

A 40-year-old man with rectal bleeding and a familial history of FAP (mother, sister, and brother) was admitted for surgical treatment in December 1985. Colonoscopy showed multiple colorectal adenomatous polyps and a tumor in the upper rectum. Routine preoperative staging with CT showed no evidence of metastasis.

As a result, he underwent a restorative proctocolectomy with mucosectomy, construction of an ileal J pouch, and hand-sewn pouch–anal anastomosis. Technical steps were performed following oncologic principles, and rectal dissection was carried out down to the pelvic floor (up to the levator plane). With the aid of two Gelpi retractors to expose the distal rectum and anal canal, adrenaline solution was instilled into the submucosa in four quadrants. Circumferential mucosal dissection begun at the dentate line, progressing cranially toward the dissected rectum above.

Pouch–anal anastomosis was made with separated 4-0 Vicryl stitches, being temporarily defunctioned with a loop ileostomy. Histologic examination of the surgical specimen confirmed many tubular adenomas distributed through the colon and a 3-cm well-differentiated rectal adenocarcinoma situated 9 cm from the distal margin (Dukes A, Astler-Coller B1, T2N0M0). The 51 resected lymph nodes had no metastatic spread. Ileostomy closure was carried out 3 months later without operative complications. Genetic tests were not performed on this patient or his family.

He was clinically followed for 18 months, when he moved to another city and did not return to follow-up. Twelve years after surgical treatment (December 1997), he started to experience fecal blood loss. In March 1998, digital examination showed a right lateral elevated mass over a firm basis, located 3 cm from the anal margin and extending cranially to the ileal pouch.

At that time, endoscopic evaluation of the ileal pouch revealed some small polyps, which biopsy showed to be tubulovillous adenomas with moderate atypia (Fig. 1). A prior biopsy of the elevated mass disclosed a tubulovillous adenoma with severe atypia, and in a subsequent attempt under anesthesia the biopsy displayed a mucinous adenocarcinoma invading the muscular layer (Fig. 2). Abdominal CT scan and carcinoembryonic antigen levels (1.3 ng/ml) were normal.

With the diagnosis of a pouch cancer, the patient underwent pouch excision and definitive terminal ileostomy. Histologic analysis showed a 2.2-cm mucinous adenocarcinoma between the ileal and anal mucosa. Tumoral invasion extended to the muscular layer, and there was distal invasion of the anal canal through the submucosa (Dukes A, Astler-Coller B1, T2N0Mx) (Fig. 3). Resection margins were free of neoplasia, and three resected lymph nodes showed no tumor invasion. The ileal pouch mucosa presented multiple tubular microadenomas with moderate atypia.

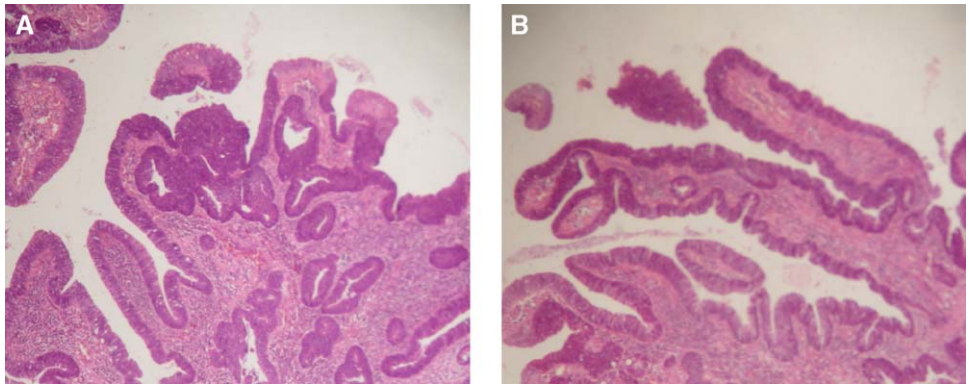

Fig. 1. Histologic aspect of pouch biopsy showing a tubulovillous adenoma with moderate atypia.

The patient has had no evidence of disease recurrence in 6 years of follow-up.

DISCUSSION

The choice of surgical treatment for FAP patients lies between the morbidity of RPC and ileal pouch-anal anastomosis (IPAA) and the mortality from rectal cancer after total colectomy and IRA.

Since its original description by Parks and Nicholls in 1978,[22] RPC with IPAA has been considered the treatment of choice for patients suffering from FAP, based on the premise that it theoretically removes all risk of intestinal malignancy and provides a better functional outcome. But the few reports of cancer after pouch surgery, including the present case, confirm that the risk of malignancy is not eliminated. Different carcinogenic mechanisms may be involved in this outcome (Table 1).

Several histologic changes have been found in the reservoir epithelium after pouch surgery. The ileal mucosa suffers metaplastic modifications toward a colonic epithelium, such as villous atrophy, inflammation, increased cell turnover, and even dysplasia, coupled with bacterial proliferation and bile salt pooling.[23] Pouch mucosa biopsies in FAP and UC patients show colonization with goblet cell multiplication, reduction or loss of villi, and increased concentration of crypts.[24] These mucosal alterations are now described as colonic phenotypic change rather than true adaptative colonic metaplasia.[25]

But even though the physicochemical conditions in the pouch may predispose its mucosa to carcinoma formation, the rarity with which pouch adenocarcinoma has been reported does not favor the hypothesis of a metaplasia-dysplasia-neoplasia sequence.[26] Certainly, the pathways of ileal pouch neoplasia in FAP differ from those in UC patients, as there are other molecular mechanisms involved.

In FAP patients, small bowel adenomas have been also found in the duodenum, jejunum, terminal ileum, and ileal mucosa after ileostomy, ileorectal anastomosis, Koch pouch, or ileoanal pouch. Although the malignant potential of noncolonic adenomas is low (with the exception of periampullary adenomas),[27] the presumption of this risk has been confirmed in papers reporting this rare but well-documented complication such as small bowel adenocarcinoma arising in ileostomy areas,[28–30] in ileoanal anastomoses,[13–15,18,20] and ileal reservoirs.[14–16,19] To our knowledge, this is the 13th case of ileal pouch cancer described in the English literature.

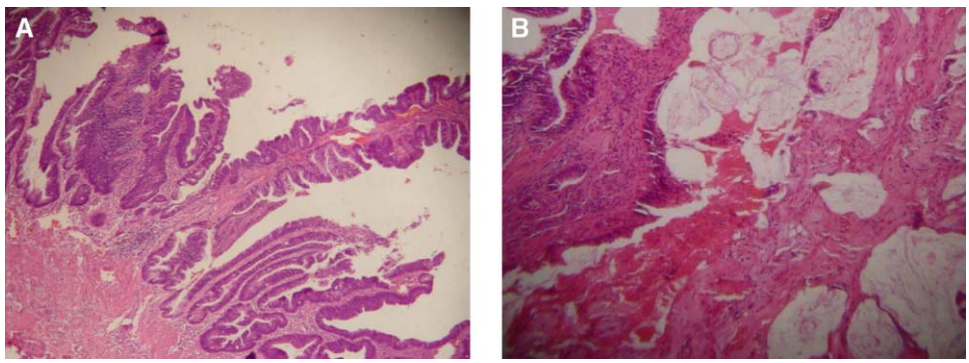

Fig. 2. Mass biopsy disclosing a mucinous adenocarcinoma with muscle layer invasion

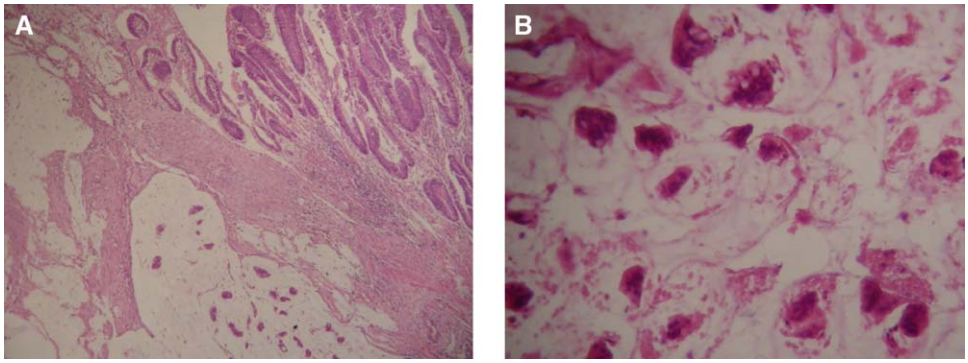

Fig. 3. Specimen pathology showing a mucinous adenocarcinoma in ileal mucosa and infiltrating the anal canal through the submucous layer.

Ileal adenomatous transformation has been considered a logical explanation for cancer arising in a restorative pouch.[18,19] The incidence of adenomatous polyps in ileal pouches has been increasingly reported in the literature, usually consisting of small tubular adenomas with mild dysplasia. No correlation between the site of APC mutation and the presence of ileal pouch adenoma has been found in most series.[6] Since the ileal pouch may represent a source of malignant transformation, regular endoscopic surveillance seems warranted until the natural history of these polyps is determined.

Parc et al.[31] found adenomas in 35% of 85 ileal pouches examined, and no invasive carcinomas were noted. The risk of developing one or more adenomas at 5, 10, and 15 years was 7%, 35%, and 75%, respectively. These authors also reported that patients with pouch adenomas were more likely to have duodenal and ampullary adenomas. This finding was not present in other series.[11,25]

In a review of 30 patients treated by RPC for FAP, Polese et al.[32] analyzed the presence of polyps in the doughnuts from stapled anastomoses (24 patients) and in the resection margins from hand-sewn anastomoses (6 patients). Surprisingly, pouch adenomas

Table 1. Adenocarcinoma in FAP after proctocolectomy and ileoanal anastomosis

Reference	Age, sex	Technique of RPC	Interval (y)	Cancer site	Treatment	Risk factor
Hochner and Metcalf[13]	34, F	Mucosectomy (straight anastomosis)	20	Anastomosis	Posterior exenteration	Multiple polyps
von Herbay[14]	33, F	Mucosectomy	8	Anastomosis	APR	Sigmoid carcinoma, pouch dysplasia
Bassuini and Billings[15]	28, M	Mucosectomy	3	Ileal pouch	APR	Not stated
Palkar[16]	39, F	Mucosectomy	5	Ileal pouch		Pouch polyps
Vuilleumier[17]	31, M	Stapled	7	Rectal cuff		Dysplasic adenoma at doughnuts
Brown[18]	37, M	Mucosectomy	7	Anastomosis	APR	Rectal carcinoma (Dukes C)
Remzi[33]	–	Stapled	–	ATZ	Redo pouch	Not stated
Cherki[19]	36, F	Mucosectomy	3.5	Ileal Pouch	RT and ileostomy	Intramucous cancer of the left colon
Ooi[20] (2 cases)	36, M	Stapled	3	ATZ	APR+RT+QT	Pouch adenoma
	41, M	Mucosectomy (straight anastomosis)	8	ATZ	Transanal excision+RT+QT	Rectal cancer and adenoma at ATZ
Vrouenraets[21] 2 cases	48, F	Stapled	8	Anastomosis	RT+APR	Adenoma in distal margin
	36, M	Stapled	10	Anastomosis	APR	Polyps at the anastomotic site
Present case	40, M	Mucosectomy	12	Anastomosis	APR	Multiple pouch polyps

APR = abdomino-perineal resection; RT = radiotherapy; QT = chemotherapy; ATZ = anal transitional zone.

were found in only 2 of 30 (7%) of patients, 1 of 6 hand-sewn and 1 of 24 stapled anastomoses ($P > 0.1$), 9 and 11 years, respectively, after operation. The risk of pouch adenomas after 8 years was 20% ($P < 0.05$). Moreover, there was no correlation between adenomas in the resection margins and the development of pouch adenomas. But it is important to note that the small number of patients was not enough to correctly assess whether adenomas in the resection margins could represent a risk factor for pouch polyps in FAP patients.

After a median 5.5 years of follow-up, Wu et al.[11] estimated the prevalence of adenomas in the ileal pouch as 42%. Other common features are their small size and great variation in number. The severity of colonic disease may also influence the risk of developing polyps in the anal transitional zone, as polyps were found in 40% of patients with severe disease versus in 16% of those with mild disease ($P < 0.05$).[33] The size of the pouch polyp has been also emphasized as a significant risk factor, requiring close endoscopic surveillance.[34]

Despite the amount of data regarding the incidence of pouch polyps over time, the extent of occurrence has not yet been truly established because of the variable recruitment of patients after surgery and limitations in follow-up. Moreover, further researches should confront specific genetic mutations and the risk of developing ileal polyps.

Ileal pouch cancers have been reported several years after RPC (Table 1). Palkar et al.[16] described a 39-year-old female with multiple pouch polyps who had a pouch cancer diagnosed 5 years after surgery. This patient was treated with total pouch excision and terminal ileostomy. In another report, von Herbay et al.[14] described a 33-year-old female who developed an ileal cancer in a pouch with high-grade dysplasia. She had a sigmoid carcinoma resected during pouch surgery. In 1996, Bassuini and Billings[15] described a 28-year-old man who underwent RP with anal mucosectomy in 1991 and developed lower abdominal pain, bloody stools, and weight loss 3 years later. Pouchogram showed a large polypoid tumor that biopsy revealed as an adenocarcinoma. After abdominoperineal resection, histologic examination confirmed an infiltrating adenocarcinoma of small bowel origin with positive nodes.

Most reports have described pouch cancers in patients within the fourth decade of life, at intervals varying from 3 to 10 years. As an exception, Hoehner and Metcalf[13] reported in 1994 a 34-year-old patient who developed an invasive adenocarcinoma at the anastomosis 20 years after proctocolectomy with straight ileoanal anastomosis. The pouch cancer described in the present article was diagnosed 12 years after the initial surgery.

This unfortunate outcome has also been associated with the presence of a malignant tumor in the resected specimen during pouch surgery. But the development of a cancer as the result of implantation of tumor cells of the primary CRC into the ileal pouch at the time of the operation is controversial. Although some papers[14,18–20] have reported patients with sigmoid and rectal adenocarcinomas with some degree of dysplasia, this fact does not explain the long interval between the first operation and the appearance of pouch cancer. In these reports, pouch cancer was diagnosed more than 7 years after the initial operation. Our patient also presented with a previous rectal cancer treated at the first operation 12 years before, and this tumor is unlikely to be associated with the further cancer the patient developed in the pouch.

Some technical aspects regarding pouch surgery have also been implicated in cancer development. Although the choice of surgical management (stapled vs. hand-sewn anastomosis) is still controversial, the hand-sewn ileal pouch-anal anastomosis with a mucosectomy of the anal transitional zone appears to reduce cancer risk.[35] Anal mucosectomy was rationalized in an attempt to exclude residual rectal mucosa in the rectal cuff or at the anastomosis.

However, Park's procedure demands technical skills and carries the risk of an incomplete mucosectomy. Residual islets of primary rectal mucosa have been detected in up to 20% of excised pouches,[36] and extensive regeneration of rectal mucosa may occur even after mucosal proctectomy.[37] As every colorectal cell in FAP carries the germ-line mutation in the APC gene, any islets of columnar epithelium left behind expose the patient to a risk of later malignant transformation.[12]

Regarding the tumor described in the present paper, our pathologist (V.R.) found a mucinous adenocarcinoma located between the ileal and anal canal mucosa. She considered the possibility that the neoplasia developed from a remnant rectal mucosa, destroying it while growing. Progressively, it invaded the anal canal through the submucosa. Although this tumor could also represent the malignant evolution of a pouch adenoma, the histologic aspects support the first hypothesis.

The development of cancer despite mucosectomy has also been documented in other reports.[13–15,18–20] In Singapore, Brown et al.[18] reported on a 37-year-old male patient who was operated for FAP associated with a rectal adenocarcinoma situated 7 cm from the anal verge. Seven years after RPC, mucosectomy, and hand-sewn anastomosis, he presented with anal pain and pus discharge due to an adenocarcinoma at the anastomotic ring associated with perianal abscess.

The authors stated that the cancer arose from retained mucosa beneath the ileoanal cuff, and it was not present or at least palpable 6 months previously. The rapid progress of the tumor was due to the lack of normal anatomical barriers; therefore, awareness of this possibility is essential for early detection.

On the other hand, many pouches are currently performed with the double-stapled technique without mucosectomy, in which the preservation of the anal canal mucosa is thought to provide better functional outcome. This technical option is claimed to be safer and simpler than the hand-sewn anastomosis with mucosectomy. The anal transitional zone (ATZ) is an area situated between the columnar epithelium of the rectum and the squamous epithelium of the anal canal. It has been claimed that its preservation leads to a fine control of continence and the ability to discriminate gas from stools.[38,39]

However, the above rectal epithelium crosses the ATZ and forms digitations within 1 cm of the dentate line in a significant proportion of patients.[40] Therefore, the stapled procedure requires a long-term follow-up of this area because of the risk of dysplasia and malignancy.

To solve this problem, it has been proposed to perform a complete mucosectomy starting at the dentate line[9] or make the hand-sewn anastomosis on the dentate line after rectal eversion and total proctectomy.[41] The authors of these papers claim that the total proctectomy avoids both problems (incomplete mucosectomy and ATZ preservation) and gives similar long-term functional results. However, there is little agreement on whether it is possible to achieve complete mucosectomy in practical terms, as some of the pouch cancers were diagnosed in mucosectomy patients.[13–16,18–20]

Until now, there is little information regarding the potential risk of ATZ. It was estimated that the risk of developing polyps at the anastomotic site is greater in the stapled (31% vs. 10% at 7 years) when compared to the hand-sewn pouch.[42] Remzi et al.[33] compared the outcomes after mucosectomy and hand-sewn IPAA (42 patients) with those after stapled IPAA (77 patients). After an average follow-up of 5.8 and 3.6 years, respectively, pouch adenomas developed in 21.4% and 10.5% in each group. In addition, they also found a 14% and 28% incidence of adenomas in the ATZ, respectively. One of the patients with staples developed cancer in the residual low rectum (5 cm) that required further resection. This patient was an obese male with a narrow pelvis. They concluded that although stapled IPAA has a better functional outcome, this advantage should be balanced against a 28% incidence of adenomas in the ATZ.

Ooi et al.[20] reported two ATZ cancers after RPC. In one patient, the tumor was diagnosed 3 years after a double-stapled anastomosis, whereas the other developed the cancer 8 years after a straight ileoanal anastomosis with mucosectomy. Both patients had previously undergone surgery elsewhere. The authors emphasized the presence of pouch tubular adenoma and rectal adenocarcinoma as risk factors in these patients.

Vuilleumier et al.[17] reported a 31-year-old male patient who presented with right inguinal and perianal pain 7 years after RPC for FAP. A diagnosis of invasive columnar cuff carcinoma was made.

Another two cases of cancer at the anastomotic site were described after the double-stapled technique.[21] It is interesting to note that in 1991 one female patient had her first operation at an older than usual age (39 years), when the specimen presented three foci of adenocarcinoma in the rectosigmoid (T3N0) and some tubular and tubulovillous adenomas at the distal margin. Besides this, she refrained from follow-up for several years and returned 8 years later with a fistula at the anastomotic site, in which biopsies revealed an infiltrative T2N0M0 adenocarcinoma. She was treated with preoperative radiotherapy (60 Gy), abdominoperineal resection, and a permanent ileostomy.

The other patient was a 27-year-old male who had surgery in 1990 and underwent endoscopy every 2 years. Ten years after surgery, an endoscopic biopsy revealed a T4N0M0 adenocarcinoma. Treatment consisted of abdominoperineal resection with partial resection of the prostate and a permanent ileostomy.

Taking into account all the aspects presented here, the discussion about the choice of anastomosis is a complex problem that is far from resolution. Considering the more frequent appearance of ATZ adenomas after double-stapled anastomosis,[11] there is a suggestion that manual anastomosis assures a more complete and accurate mucosectomy.[43] Otherwise, double-stapled anastomosis is quicker, easier, and presents lower morbidity with better function,[44] advantages that outweigh the problem of leaving a little extension of ATZ in some patients. Furthermore, the ATZ area can be easily surveyed and stripped out when necessary.

Flexible endoscopy with bowel preparation is required for diagnosis and removal of the polyps. Once detected, pouch polyps should be managed with cyclooxygenase inhibitors, fulguration, and local resection or partial mucosectomy, depending on their number, location and size.[20,25,33]

Although endoscopic screening and surveillance programs for these lesions have not yet been defined, recommendations exist for regular surveillance at a

frequency similar to that of upper gastrointestinal endoscopy.[31] Other proponents have suggested annual flexible pouchoscopy, followed by reassessment 6 months after the polyp has been detected.[19–21,33] Some have proposed a 3-year interval when there are no polyps in the pouch, 2 to 3 years when polyps are found, and frequent follow-up in the cases of large or carpeting polyps.[25]

Pouch adenomatosis with severe dysplasia is probably the most difficult situation. Medical treatment with sulindac,[44] laser destruction, and frequent checking of the pouch by endoscopy or pouch excision are the available options.

Cases of high-grade dysplasia or in situ carcinoma arising in a remnant rectal stump may be managed conservatively, by completing the mucosectomy via a perineal approach by pouch advancement and neo-ileoanal anastomosis.[45,46] Otherwise, the presence of an invasive cancer in a pouch will require pouch excision and ileostomy. Neoadjuvant chemoradiotherapy must be indicated as a case-by-case basis.

CONCLUSION

For the moment, the present review suggests a high prevalence of adenoma formation in pouches and, as pouch endoscopy is not routine during follow-up, the incidence of polyps after RP has probably been underestimated so far. Thus longer follow-up will be needed to elucidate their natural history and the associated risk of carcinoma.

The cumulative risk of developing polyps and carcinoma at the pouch and at the anastomotic site increases with time. Considering that RPC has been performed for more than two decades and that the number of cancer cases already reported is still small, one may suppose that this risk is undoubtedly small, although a longer follow-up may clarify this question. Some high-risk factors for cancer at the time of IPAA have been suggested, such as multiple pouch polyps, polyp size and age, incomplete mucosectomy, and preservation of the ATZ.

After RPC, cancer may arise in the ileal pouch itself and in the ATZ either after stapled technique or mucosectomy with hand-sewn anastomosis. Adenomas arising on remnant rectal mucosa have a much higher risk of malignant transformation than those adenomas found on the ileal mucosa of the pouch. This is in accordance with the fact that only three cases of pouch cancers have been described until now. In addition, patients with double-stapled anastomosis may require closer follow-up, especially those with severe colonic disease.

These ideas strengthen the recommendation for careful and long-term surveillance of FAP patients after RPC, regardless of anastomotic technique.[11,13,17,42,43]

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Selective Inhibition of Endothelin Receptor A as an Anti-angiogenic and Anti-proliferative Strategy for Human Pancreatic Cancer

Sarah Bhargava, Ph.D., Till Stummeyer, Birgit Hotz, O. Joe Hines, M.D., Howard A. Reber, M.D., Heinz J. Buhr, M.D., Hubert G. Hotz, M.D.

Endothelin-1 (ET-1) plays a major role in tumor proliferation and angiogenesis of various types of cancer acting through endothelin receptors A and B (ET_RA and ET_RB). The aim of this study was to analyze the ET-1/ET_R system in human pancreatic cancer cell lines and to evaluate the effect of a selective endothelin A inhibitor in vitro and in vivo in an orthotopic mouse model. Three different human pancreatic cancer cell lines, MiaPaCa-2, AsPC-1, and Panc-1, were studied. We found that proliferation of human pancreatic carcinoma cells expressing ET_RA was significantly reduced with a selective antagonist. Hypoxic conditions led to improved results compared to a normoxic environment (MiaPaCa-2: −53% vs. −18%; AsPC-1: −54% vs. −46%). Proliferation of ET_RA negative Panc-1 cells was not decreased. In vivo, the selective ET_RA inhibition resulted in reduced angiogenesis as measured by lower microvessel densities (MiaPaCa-2: −47%; AsPC-1: −55%). The blockade of ET_RA decreased the volume (MiaPaCa-2: −87%; AsPC-1: −28%) and metastatic spread (MiaPaCa-2: −95.5%; AsPC-1: −27%) of receptor-positive tumors, thereby increasing survival in experimental pancreatic cancer. ET_RA blockade did not show an effect on ET_RA negative Panc-1 tumors. Therefore, targeting ET_RA with a selective antagonist might provide a new approach to reducing proliferation and angiogenesis in human pancreatic cancer. (J Gastrointest Surg 2005;9:703–709)

Key words: Pancreatic cancer, endothelin-1, vascular endothelial growth factor, angiogenesis

INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer-related death in Western countries. Its overall 5-year survival rate of less than 5%[1] did not improve in the past three decades. Currently, surgical resection presents the only curative approach to this disease. Because of the late appearance of symptoms, more than 80% patients are diagnosed with pancreatic cancer at a locally advanced or metastatic stage when surgery is not feasible.[2] Even after curative resection, most patients will succumb to local tumor recurrence and/or distant metastasis.[2,3] The response of pancreatic cancer and its metastases to conventional therapies like radio- and chemotherapy is poor.[4] Therefore, there is a need for additional studies to target better therapeutic strategies.

Endothelin-1 (ET-1) is a multifunctional cytokine derived from endothelial cells that is known to regulate vasoconstriction. This peptide is also supposed to contribute to proliferation of tumor cells and to the process of tumor angiogenesis.[5,6] It plays a major role in mitogenesis and is produced by cell lines from numerous cancers, including human pancreatic cancer.[7] Previous studies have demonstrated that various human pancreatic cancer cell lines express mRNA for ET-1. It has also been shown that pancreatic cancer cells produce ET-1 protein, which is then released into the media.[8] The biological function of ET-1 is mediated via the endothelin receptors A (ET_RA) and B (ET_RB).[9] Previous studies indicate that activation of endothelin receptors increases cell proliferation, inhibition of apoptosis, and remodeling of

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From the Department of Surgery, Charité–Medical School Berlin (S.B., T.S., B.H., H.J.B., H.G.H.), Campus Benjamin Franklin, Berlin, Germany; and Department of Surgery, UCLA School of Medicine (O.J.H., H.A.R.), Los Angeles, California.
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Reprint requests: Dr. Hubert G. Hotz, Chirurgische Klinik I, Charité–Medical School Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, D-12200 Berlin, Germany. e-mail: hubert.hotz@charite.de

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the surrounding matrix, thereby enabling an enhanced tumor progression.[10] It has been shown that ET-1 acts in an autocrine stimulatory way selectively through ET_RA[11] and also stimulates the production of vascular endothelial growth factor (VEGF), the main regulator of angiogenesis.[12,13] ET_RA blockade inhibits in vitro growth of ovarian carcinoma, cervical carcinoma, colon carcinoma cells, and Kaposi's sarcoma cells.[14–17] This has also been demonstrated in vivo with xenograft models for carcinoma of the ovary and cervix and for Kaposi's sarcoma.[18–20] Furthermore, antagonizing ET_RA as a monotherapy in men with hormone-refractory prostate cancer exhibited encouraging results in a clinical phase II study.[21]

The functional role of the endothelin system in pancreatic cancer has not yet been elucidated. The aim of the present study was therefore to assess the expression of ET-1 and endothelin receptors A and B in human pancreatic cancer cell lines. To determine the therapeutic potential of the selective ET_RA inhibition, we tested the in vitro effects on proliferation of the tumor cells. The effects of the selective antagonist on tumor growth and angiogenesis were further studied in vivo in a clinically relevant orthotopic nude mouse model of human pancreatic cancer by analyzing the tumor microvessel densities.

MATERIALS AND METHODS

Drugs

For in vitro assays and intraperitoneal injection, LU-302146 (Knoll AG, Ludwigshafen, Germany), a selective ET_RA receptor antagonist, was dissolved in different concentrations (10^{-9} to 10^{-6} M) in 0.9% NaCl (pH 7.5). Endothelin-1 (BioTrend, Cologne, Germany) was suspended in PBS (pH 7.5) to the final concentrations of 10^{-9} to 10^{-7} M.

Cell Lines and Culture Conditions

The following human pancreatic adenocarcinoma cell lines were obtained from the American Type Culture Collection (Rockville, MD): MiaPaCa-2 (undifferentiated), AsPC-1 (poorly to moderately differentiated), and PANC-1 (poorly differentiated).[22] MiaPaCa-2 cells and PANC-1 cells were cultured in Dulbecco modified Eagle's medium (DMEN; Gibco, Grand Island, NY), and AsPC-1 cells were cultured in RPMI-1640 medium (Gibco). All media were supplemented with 10% heat-inactivated fetal bovine serum (FBS; Gibco), penicillin G (100 U/ml), streptomycin (100 µg/ml), and 0.1% fungizone (Gibco). The cells were incubated at 37°C in humidified air with 5% CO_2. The medium was replaced twice weekly, and cells were maintained by serial passaging after trypsinization with 0.1% trypsin.

Reverse Transcriptase Polymerase Chain Reaction (PCR)

Total cellular RNA was extracted from cell cultures using TRIzol (Invitrogen, Karlsruhe, Germany) according to the manufacturer's instructions and resuspended in 10 µl of DMPC-treated water. RNA concentration was determined using a BioPhotometer (Eppendorf Scientific, Hamburg, Germany). Total RNA (2 µg) was primed with an oligo(dT) oligonucleotide and reverse-transcribed with M-MLV reverse transcriptase and dNTPs (Promega, Mannheim, Germany) according to the manufacturer's instructions. First-strand cDNA was amplified with transcript-specific oligonucleotides using ReadyMix Taq PCR Reaction Mix (Sigma-Aldrich, Seelze, Germany). The primers (TIB MOLBIOL, Berlin, Germany) for the respective genes were designed as follows: ET-1 (sense: 5′- TGC TCC TGC TCG TCC CTG ATG GAT AAA GAG-3; antisense: 5′- GGT CAC ATA ACG CTC TCT GGA GGG CTT-3′), ET_RA (sense: 5′- CAC TGG TTG GAT GTG TAA TC-3′; antisense: 5′- GGA GAT CAA TGA CCA CAT AG-3′), ET_RB (sense: 5′- TGA ACA CGG TTG TGT CCT GC-3′, antisense: 5′- ACT GAA TAG CCA CCA ATC TT-3′). PCR products and a 1 kb DNA molecular weight marker were then electrophoresed on a 1% agarose gel; the gel was then visualized and photographed under ultraviolet light.

In Vitro Assessment of Cell Proliferation

All cell lines were exposed to LU-302146 under normoxia or hypoxic (0% O_2, 95% N_2, 5% CO_2) conditions using a hypoxia chamber (Billups-Rothenberg, Del Mar, CA). To examine the effect of LU-302146 on in vitro cell proliferation, 2×10^5 cells from each cell line were seeded in six-well culture plates in 2 ml of the respective cell culture medium. The medium was changed the next day (day 1), and LU-302146 was added in the following concentrations: 1nM, 10 nM, 100nM, and 1000 nM. After 72 hours (day 4), the cells were trypsinized and counted in a standard hemocytometer.

Laboratory Animals and Orthotopic Implantation Technique

Four-week-old male nude mice (Crl:NU/NU-*nu*BR) weighing 20 to 22 g were obtained from Charles River Laboratories (Wilmington, MA). The animals were housed in microisolator cages with

autoclaved bedding, food, and water. The mice were maintained on a daily 12-hour light/12-hour dark cycle. All experiments were conducted in accordance with the national guidelines for the care and use of laboratory animals, and the experimental protocol was approved by the Chancellor's Animal Research Committee of the University of California, Los Angeles.

The orthotopic pancreatic tumor implantation technique was previously described in detail.[23] 5×10^6 cells of each human pancreatic cancer cell line were injected subcutaneously into the flanks of donor nude mice. The animals were sacrificed after 3 to 4 weeks, when the subcutaneous tumors had reached a size of 1 cm in the largest diameter. The donor tumors were harvested and minced by a scalpel (no. 11) into fragments of 1 mm^3 in size. The abdomen of the anesthetized tumor-recipient nude mouse was opened by a midline incision under aseptic conditions at a laminar air flow working bench, and the pancreatic tail with the spleen was gently exteriorized. Two small tissue pockets were prepared in the pancreatic parenchyma as an implantation bed with a microscissor (RS-5610 VANNAS; Roboz, Rockville, MD). One donor tumor fragment was placed into each pancreatic tissue pocket in a way that the tumor tissue was completely surrounded by pancreatic parenchyma. The pancreas was relocated into the abdominal cavity, which was then closed in two layers with 5-0 absorbable sutures (DEXON "S"; Davis+Geck, Manati, Puerto Rico).

In Vivo Treatment with LU-302146

Forty-eight recipient animals (8 nude mice per pancreatic cancer cell line) were randomly allocated into one treatment and one control group. Treatment with LU-302146 was started 3 days after orthotopic tumor implantation. The therapeutic substance was administered daily by gavage with a dosage of 30 mg/kg over a period of 14 weeks. The control group received the carrier substance (0.9% NaCl). The mice were monitored daily for their clinical condition, weighed weekly, and sacrificed 14 weeks after the orthotopic tumor implantation by a lethal dose of sodium pentobarbital (0.5 mg/g).

All animals underwent an autopsy at the end of the observation period. The perpendicular diameters of the primary orthotopic tumor were measured with calipers, and the volume was calculated using the following formula: volume = length × width × depth/2. A dissemination score was developed to assess local tumor infiltration as well as distant metastasis.[23] Local infiltration was determined at the following sites: spleen, stomach, liver (hilus), kidney (hilus), retroperitoneum, diaphragm, mesentery, bowel loops, and abdominal wall. Isolated tumor nodules with no anatomical connection to the primary were judged as distant metastases. The sites of evaluation included liver, kidney, spleen, lung, diaphragm, mesentery, retroperitoneum, mediastinum, and the suture line. Tumor dissemination was quantified as follows: every manifestation of tumor infiltration or metastasis was credited with one point. Additional points were awarded for massive local infiltration (e.g., including more than half of the circumference of the spleen), multiple metastatic nodules (>1 in parenchymal organs; >10 on diaphragm, mesentery, or retroperitoneum), and metastatic nodules larger than 50 mm^3. Clinical consequences of the tumor growth were incorporated into this scoring system: formation of ascites (2 points if volume >5 ml) and development of jaundice, ileus, and cachexia. The autopsy data were analyzed by one individual (HGH) who was blinded to the treatment groups.

The primary tumor and all sites of potential infiltration or metastasis were harvested, fixed in paraformaldehyde, and embedded in paraffin. Five-micron thin-tissue sections were obtained and stained with hematoxylin and eosin for microscopic examination. The sections were reviewed to confirm the findings of the macroscopic dissemination score.

Microvessel Density

Anti-CD31 was used as endothelial marker to highlight intratumoral microvessels. The human pancreatic cancer xenograft tumors orthotopically grown in the pancreas of nude mice were immediately fixed in 10% neutral buffered formalin and embedded in paraffin. Tissue sections (3 μm) were deparaffinized and rehydrated, and target retrieval was done by cooking tissues at 97°C for 15 min in 0.01% EDTA (pH 8.0) followed by a 5-minute treatment in a 3% hydrogen peroxide solution to block endogenous alkaline phosphatase activity. After blocking slides for 5 minutes, a purified anti-mouse CD 31 (PECAM-1) antibody (Santa Cruz, San Diego, CA) was applied in a 1:100 dilution and was incubated at 37°C for 30 minutes. After thorough rinsing in PBS-Tween solution, slides were incubated with a biotinylated secondary antibody for 20 minutes, followed by a 20-minute incubation with streptavidin peroxidase. For color development, slides were incubated for 2 minutes in DAB (3,3′-diaminobenzidine tetrahydrochloride). Microvessel density was quantified as described by Weidner et al.[24,25] Areas of highest neovascularization were found by scanning the sections at low power (40× and 100× total magnification). Individual microvessel counts were made on ten 200× fields (0.74 mm^2 per field).

Statistical Analysis

Data are presented as mean ± SEM. Continuous, normally distributed variables were analyzed by the Student's *t* test. Discontinuous variables (dissemination score, microvessel density) were analyzed by the Mann-Whitney rank sum test. Differences were considered significant at $P < 0.05$.

RESULTS

In Vitro

mRNA Expression. The three different human pancreatic cancer cell lines, MiaPaCa-2 (Fig. 1*A*), AsPC-1 (Fig. 1*B*), and Panc-1 (Fig. 1*C*), were evaluated for mRNA expression of ET-1, ET_RA, and ET_RB by reverse transcriptase PCR. The PCR products were separated on a 1% agarose gel. As a control, all three human pancreatic cancer cell lines were measured for the expression of β-actin. All cell lines expressed ET-1 at the same level. ET_RA was expressed by MiaPaCa-2 and AsPC-1 but not Panc-1 cells. ET_RB was not produced by any of the investigated cell lines.

Tumor Cell Proliferation. The effects of the selective ET_RA inhibitor on the proliferation of the three human pancreatic cancer cell lines MiaPaCa-2, AsPC-1, and Panc-1 were studied under normoxic and hypoxic conditions over a period of 72 hours (Fig. 2). The selective inhibitor LU-302146 was applied to the cell using four different concentrations: 1 nM, 10 nM, 100 nM, and 1000 nM. The ET_RA blockade resulted in a moderate reduction of proliferation in the ET_RA-positive cells, MiaPaCa-2 and AsPC-1. The selective blockade was more effective under hypoxic conditions; the highest concentration of LU-302146 (10^{-6} M) reduced cell proliferation of MiaPaCa-2 to less than half (−52.8%). Equivalent results were obtained with AsPC-1 cells (−52.2%). Panc-1 was not affected by the addition of LU-302146 at either normoxic or at hypoxic conditions.

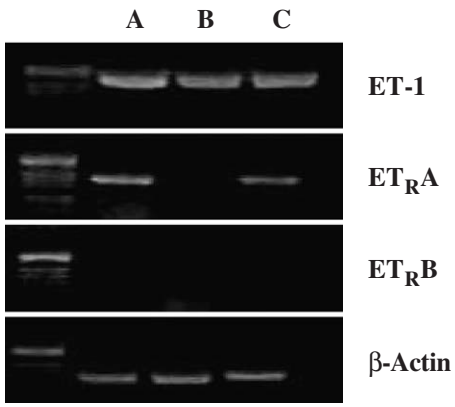

Fig. 1. One representative 1% agarose DNA gel of the RT-PCR products for ET-1 (462 bp), ET_RA (366 bp), ET_RB (530 bp), and β-Actin (336 bp) in human pancreatic cancer cell lines MiaPaCa-2 (**A**), Panc-1 (**B**), and AsPC-1 (**C**). ET_RA is expressed only by MiaPaCa-2 and AsPC-1, whereas none of the pancreatic cancer cell lines produced ET_RB.

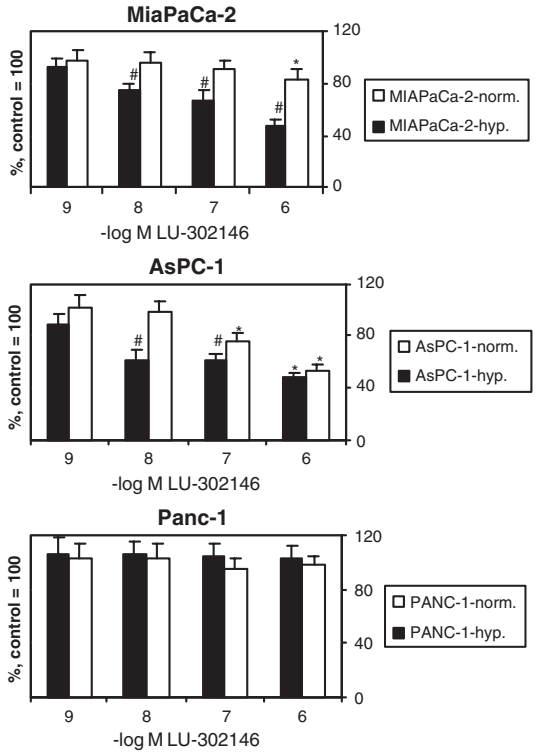

Fig. 2. Effect of selective ET_RA blockade on proliferation of pancreatic cancer cells under either normoxic (□) or hypoxic conditions (■). A dose-dependent effect of LU-302145 on MiaPaCa-2 and AsPC-1 can be observed, which is more prominent under hypoxia. Panc-1 cells are not influenced (* = $p < 0.05$ vs. control, # = $p < 0.05$ vs. normoxic).

In Vivo

Volumes of Primary Tumors. In vivo treatment with the selective ET_RA inhibitor LU-302146 resulted in significant reductions of the size of tumors derived from ET_RA-positive MiaPaca-2 and AsPC-1 cells (Fig. 3*A*). The highest decrease was observed at MiaPaCa-2 tumors, with approximately a tenth of the initial tumor volume (482 mm^3 ± 247 mm^3 vs. 3676 mm^3 ± 285 mm^3; $P < 0.05$). AsPC-1 tumors were reduced to two-thirds of tumor size by treatment with LU-302146 (1248 mm^3 ± 152 mm^3 vs. 1733 mm^3 ± 213 mm^3). The mean tumor volumes did not differ in the Panc-1 group expressing no ET_RA (2732 mm^3 ± 415 mm^3 vs. 2629 mm^3 ± 484 mm^3).

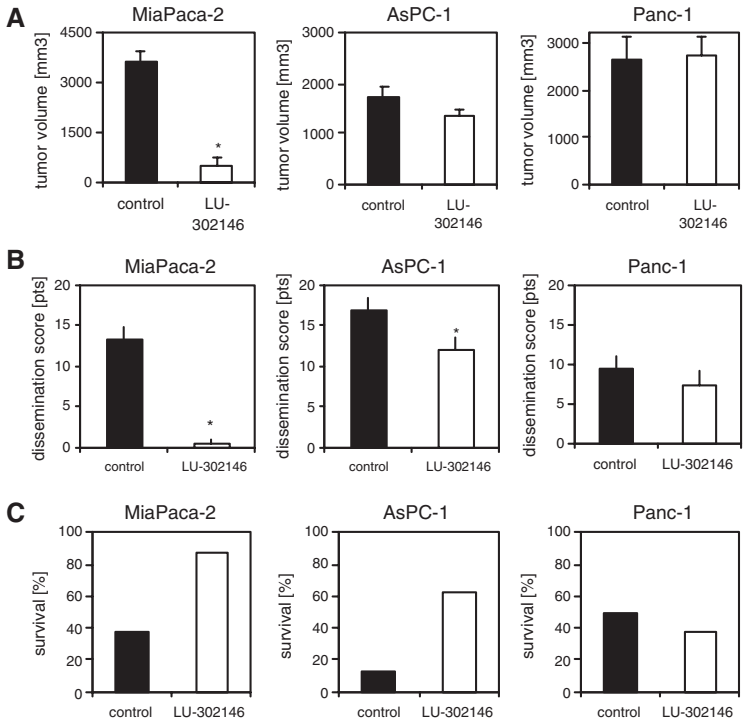

Fig. 3. Tumor volume (**A**), dissemination scores (**B**), and survival (**C**) in LU-302145-treated (□) and untreated (■) animals bearing tumors derived from human pancreatic cancer cell lines (* = $p < 0.05$ vs. control).

Tumor Dissemination. For comparing the groups in terms of tumor spread, we used mean scores. Treatment with LU-302146 resulted in a statistically significant reduction of tumor spread in the groups with tumors expressing ET_RA (Fig. 3*B*). The incidence of local infiltration and distant metastasis in the control group was significantly higher than in the LU-302146-treated group with MiaPaCa-2 tumors (0.6 ± 0.5 vs. 13.3 ± 1.4; $P < 0.05$). In the AsPC-1 group, the mean dissemination score diminished from 16.9 ± 1.3 points to 12.1 ± 1.3 points ($P < 0.05$). There were no significant differences regarding the dissemination score in the Panc-1 groups (controls, 9.5 ± 1.7; LU-302146, 7.5 ± 1.8).

Survival. The MiaPaCa-2 and AsPC-1 tumors showed a relative aggressive behavior in vivo, which was reflected in a low 14-week-survival of the controls (37.5% and 12.5%, respectively), but because of the limited number of animals in each group (n = 8), this difference was not statistically significant (Fig. 3*C*). Therapy with LU-302146 revealed a trend to increased survival rates in both groups (87.5% and 62.5%). Survival rates of mice with Panc-1 tumors did not differ considerably (37.5% vs. 50%) in the treated and untreated group.

Microvessel Density

As a parameter of angiogenic activity, the microvessel density was determined by immunohistochemistry using Anti-CD31 as an endothelial marker. The ET_RA-positive tumor tissue samples collected from treated animals revealed a significantly decreased rate of microvessels compared to tissue of untreated animals (MiaPaCa-2: 32.9 ± 3.8/0.74 mm^2 vs. 70.0 ± 4.2; AsPC-1: 43.0 ± 3.0 vs. 77.6 ± 4.2/0.74 mm^2; $P < 0.05$) (Fig. 4). The microvessel densities of the tumors of ET_RA-negative Panc-1 cells were not significantly affected by treatment with LU-302146 (Panc-1: 60.3 ± 5.4 vs. 69.5 ± 3.6; $P < 0.05$).

DISCUSSION

Pancreatic cancer is a highly malignant and devastating disease. Novel therapeutic approaches are needed, since surgery cures only few patients and radiation and chemotherapy are of limited effects. Pancreatic cancer is characterized by high microvessel densities compared to the tissue area of normal pancreas, a result of the overexpression of mitogenic and angiogenic factors.[26] Therefore, targeting the angiogenesis of pancreatic cancer presents a promising anticancer strategy.

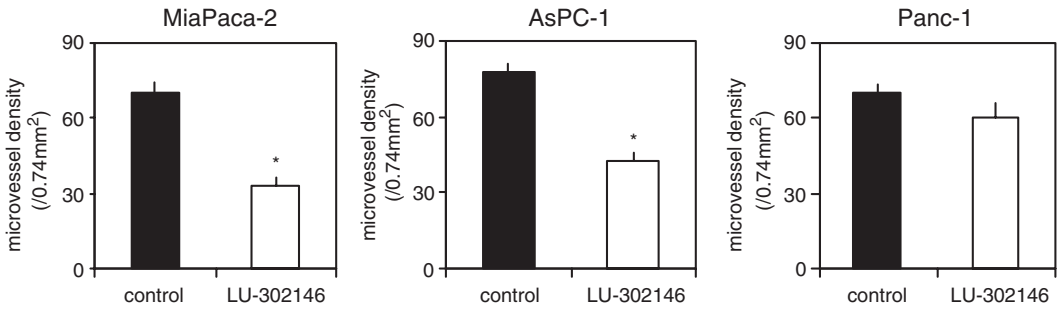

Fig. 4. Microvessel density as determined by CD31 immunostaining. LU-302146 treated animals (□) bearing MiaPaCa-2 and AsPC-1 tumors had significantly fewer microvessels as compared to untreated animals (■), Panc-1 tumors were not influenced (* = $p < 0.05$ vs. control).

Endothelin and its receptors, referring to the endothelin axis, are involved in tumorigenesis and tumor progression.[6] ET-1 acts as an autocrine growth factor on endothelial cells and stimulates neovascularization.[27] Recent findings showed that increased expression rates of ET-1 and its receptors are linked to elevated microvessel densities.[28] The use of ET_RA antagonists seems to be an attractive approach because the selective inhibition of ET_RA reduces both tumor cell proliferation and angiogenesis in different tumor types.[18] Rosano et al. established the reduction of cell proliferation and angiogenesis by applying an ET_RA antagonist (ABT-627) to ovarian cancer.[19] Similar antitumoral effects have been achieved within prostate cancer.[21]

Previous studies showed that ET-1 is produced by numerous human pancreatic cancer cell lines.[7] In view of this, the present study analyzed the ET-1 system in pancreatic cancer and also studied the effects of the selective blockade on tumor cell proliferation and tumor angiogenesis.

In our analysis we successfully confirmed this, and moreover showed that mRNA expression of ET_RA is limited to some cell lines (MiaCaPa-2 and AsPC-1, not Panc-1), while ET_RB is not produced by the investigated pancreatic cell lines. In vitro assays demonstrated that the ET_RA antagonist LU-302146 reduces proliferation of human pancreatic cancer cells carrying ET_RA. As expected, ET_RA-negative cells were not influenced by the presence of the inhibitor.

Pancreatic cancer is a devastating malignancy with a variety of alterations that lead to invasive and metastatic tumor growth. The reasons for the aggressive nature are poorly understood. As shown by intraoperative needle measurement, adenocarcinoma of the pancreas presents with significant hypoxia. Those high levels of hypoxia are assumed to promote the malignant progression and outstanding aggressiveness of this disease.[29,30] Recent studies indicate that hypoxia causes genomic alterations and can result in an increased resistance toward chemo- and radiation therapy. Intratumoral hypoxia acts as a physiological stimulus for ET-1, improving the angiogenic phenotype.[28] We suggest that the specific inhibition of increased ET-1 levels enhances the anti-proliferative effects under hypoxic conditions. For that reason we compared the inhibitory effect of LU-302146 under normoxic and hypoxic conditions. We found that the antagonist reduced tumor cell proliferation under hypoxic conditions more efficiently than within normoxic cells. Consequently, the hypoxia-induced growth of pancreatic cancer cells seems to be regulated at least in part via ET-1 and ET_RA.

For evaluating the effects of ET_RA blockade in vivo we used an orthotopic nude mouse model.[23] We found that administration of LU-302146 reduced tumor volume in ET_RA-positive tumors. Tumor volumes of the MiaCaPa-2 group were significantly decreased, and those of the AsPC-1 group tended to be reduced. Similar results were obtained concerning local infiltration and metastatic spread. Dissemination scores were fundamentally decreased to lower than 5% in the treated MiaPaCa-2 group compared to untreated group. Within the AsPC-1 group, the score was reduced to 70%. Receptor-negative tumors (Panc-1) were not influenced by application of the antagonist. These results can be assigned to survival rates with an increasing tendency from 37% to 87% in the MiaPaCa-2 group and from 12% to 62% in the AsPC-1 animals. Angiogenesis was estimated by determining microvessel densities using an anti-CD31 antibody for immunohistochemical staining. The reduced microvessel density in primary tumors indicated an anti-angiogenic effect of the selective ET_RA blockade with LU-302146 in receptor positive tumors.

CONCLUSION

We conclude that endothelin-1 plays a role in the angiogenesis and tumor cell proliferation of human pancreatic cancer. The current analysis represents the first study for an anti-angiogenic and anti-proliferative approach by selective inhibition of ET_RA in pancreatic cancer cells. We demonstrated that the selective blockade exhibits therapeutic efficiency in a clinical relevant orthotopic mouse model, which is associated with diminished tumor volumes, systemic spread, and a substantially reduced microvessel density. In view of these findings, future studies on the clinical application of endothelin receptor antagonists for ET_RA-positive pancreatic cancers seem to be warranted.

Dedicated to the 60th birthday of Heinz J. Buhr.

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Surgical Treatment of Pancreas Divisum Causing Chronic Pancreatitis: The Outcome Benefits of Duodenum-Preserving Pancreatic Head Resection

W. Schlosser, M.D., B. M. Rau, M.D., B. Poch, M.D., H. G. Beger, M.D.

Pancreas divisum (PD) represents a duct anomaly in the pancreatic head ducts, leading frequently leading to recurrent acute pancreatitis (rAP) or chronic pancreatitis (CP). Based on endoscopic retrograde cholangiopancreatography, pancreas divisum can be found in 1% to 6% of patients with pancreatitis. The correlation of this abnormality with pancreatic disease is an issue of continuing controversy. Because of the underlying duct anomalies and major pathomorphological changes in the pancreatic head, duodenum-preserving pancreatic head resection (DPPHR) offers an option for causal treatment. Thirty-six patients with pancreatitis caused by PD were treated surgically. Thirty patients suffered from CP, 6 from rAP. The mean duration of the disease was 47.5 and 49.8 months, respectively. The age at the time of surgery was 39.2 years in the CP group, and 27.6 years in the rAP group. Median hospitalization since diagnosis was 18.8 weeks for CP patients and 24.6 weeks for rAP patients. Previous procedures performed in these patients included endoscopic papillotomy (30%), duct stenting (14%), and surgical treatment (17%). The median preoperative pain score was 8 on a visual analog scale. According to the classification of pancreas divisum, 10 patients demonstrated a complete PD, 25 had a functionally incomplete PD, and 1 had a dorsal duct type. The pain status as well as the endocrine (oral glucose tolerance test) and exocrine (pancreolauryl test) function were evaluated preoperatively and early and late postoperatively with a median follow-up time of 39.3 months. There was no operative-related mortality. The follow-up was 100%; 4 patients died (1 from suicide, 1 from cardiac arrest, and 2 from cancer of the esophagus). Fifty percent of the patients were completely pain-free, 31% had a significant reduction of pain with a median pain score of 2 ($P < 0.001$). Six patients (5 CP, 1 rAP) had further attacks of acute pancreatitis with a need for hospitalization. DPPHR reduced pain and preserved the endocrine function in the majority of patients with pancreas divisum. Therefore, DPPHR is an alternative to other resective or drainage procedures after failure of interventional treatment. (J GASTROINTEST SURG 2005;9:710–715)

KEY WORDS: Chronic pancreatitis, pancreas division, duodenum-preserving pancreatic head resection

Pancreas divisum (PD) is the most common congenital anomaly of the pancreas. In autopsy studies, PD is found in 4% to 14% of patients;[1–3] on the basis of endoscopic retrograde cholangiopancreatography documentation, PD has been identified in up to 6%.[2,4,5] However, PD is found in up to 25% of patients with acute idiopathic pancreatitis.[1,6,7]

The clinical appearance of PD is characterized by the development of pancreatitis in individuals with high-grade PD anomalies.[1,8,9] Most frequently, a dorsal duct hypertension secondary to inadequate flow through a narrowed segment of the duct of Santorini and/or the papilla leads to chronic pancreatitis (CP).[4,10] In addition, recurrent acute pancreatitis (rAP) without pathologic endo- and exocrine pancreatic function and pathomorphological signs of CP is causally linked to the presence of PD.[7] In some patients the presence of PD is the leading pathomorphological factor, but additional injuries such as alcohol overconsumption are needed for the development of rAP or finally CP. Many endoscopic interventional and surgical procedures, such as endoscopic dilatation, papillotomy and stent implantation, sphincteroplasty, or even surgical duct drainage, have been employed to prevent or

From the Department of General Surgery, University of Ulm (W.S., B.M.R, H.G.B.), Ulm, Germany; Department of Visceral Surgery, Illertalklinik (B.P., H.G.B.), Germany; and Department of General-, Vascular-, and Transplantation Surgery, University of Saarland, Homburg/Saar, Germany. Reprint requests: Prof. em. Dr. H. G. Beger, c/o Universitätsklinikum Ulm, Steinhövelstrasse 9, 89075 Ulm, Germany. e-mail: hans.beger@medizin.uni-ulm.de

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improve the acute or chronic inflammatory changes of PD.[1–4] Only a few studies have reported improvement of pain and a reduction of pancreatic episodes after endoscopic interventional treatment.[11–15] In most, including recent prospective series, only a short-lasting improvement has been reported.[11,16,17] Since PD is a disease of the duct system in the pancreatic head that usually causes CP, duodenum-preserving pancreatic head resection (DPPHR), which has led to evident long-lasting eradication of pain as well as improvement of clinical symptoms and pancreatic functions in patients with chronic alcoholic pancreatitis, offers the potential to contribute significantly to the successful management of patients with PD.[18,19]

In this study we report the short- and long-term follow-up results in a group of 36 patients suffering from CP or rAP due to PD, using DPPHR as the surgical treatment.

PATIENTS AND METHODS

Between May 1982 and February 2000, 36 patients with clinical consequences of PD were treated in the Department of General Surgery, University of Ulm. Thirty patients suffered from CP and 6 patients had rAP. Of the 36 patients, 21 were men, and the mean age was 37.9 years. The mean duration of the disease since diagnosis was 47.6 months in the CP group and 34.6 months in the rAP group.

The study and data collection were performed as a prospective trial. Thirty patients with CP and 6 patients with rAP were included on the basis of clinically, radiologically, and functionally proven disease. The diagnosis of CP and rAP was made using the case history data, exocrine and endocrine function tests, imaging procedures, and intraoperative findings as well as the histologic investigation of operative specimens. Clinical data, endocrine and exocrine function tests, and pain status were assessed pre- and postoperatively to evaluate the late outcome. For measurement of the endocrine function, an oral glucose tolerance test (OGTT) was performed, and a pancreolauryl test was used for exocrine function measurement.[20,21]

Preoperative Morbidity

The patients with CP due to PD had been hospitalized a median of 18.8 weeks per patient since diagnosis; patients with rAP had been hospitalized 24.6 weeks per patient. The patients with CP suffered 1.5 periods of acute pancreatitis per patient per year; in patients suffering from rAP, the frequency of attacks of acute pancreatitis was 2.2 per patient per year (Table 1).

On the basis of the endoscopic retrograde cholangiopancreatography and/or magnetic resonance cholangiopancreatography, a complete classic PD was observed in 10 patients (28%), 25 patients (69%) had a functionally incomplete PD, and 1 patient (3%) had a dorsal duct type. Relapsing or permanent upper abdominal pain were the main preoperative symptoms in both groups of patients. To evaluate the degree of pain, patients had to describe the intensity of pain on a visual analog scale (VAS) ranging from 0 (no pain) to 10 (maximal unbearable pain). In 8 of the patients with CP, alcohol consumption was recorded, whereas one of the patients with rAP reported alcohol consumption. Sixteen of the 36 patients reported previous interventional treatment. Up to the point of the study, 6 patients (4 with CP and 2 with rAP) had undergone surgical treatment. Two patients had had transduodenal sphincteroplasty (one in the papilla of vater and one in the minor papilla), and 4 patients had had a duct drainage procedure (Table 1).

Preoperative and Intraoperative Assessment

Twelve of the patients with CP and 4 of the patients with rAP displayed a prepapillary stenosis of the duct of Santorini. Pancreatic tissue calcification was observed in 11 of the patients with CP, and duct stones were found in 6 of the patients with CP and none of the patients with rAP. Pseudocystic lesions, exclusively developed in the head of the pancreas, were

Table 1. Treatment before surgery

Treatment	CP (n = 30)	rAP (n = 6)	Total (n = 36)
Hospitalization since diagnosis (per pt)	18.8 wk	24.6 wk	
Annual periods of acute pancreatitis (per pt)	1.5	2.2	
Endoscopic papillotomy	7	4	11 (31%)
Pancreatic duct stenting	3	2	5 (14%)
Surgical treatment up to now	4	2	6 (17%)
Annual periods of hospitalizations (per pt)	1.7	2.8	

CP = chronic pancreatitis; rAP = recurrent acute pancreatitis.

observed in 10 patients, 9 with CP and one with rAP. An inflammatory mass in the head of the pancreas was objectified in 14 patients with CP and in 1 patient with rAP. A duct dilatation of the left pancreas in the corpus and cauda was found in 12 patients, 10 with CP and 2 with rAP.

Preoperative evaluation of endocrine function using the OGTT showed an impaired glucose metabolism in 13 (36%) of the patients; 2 of these patients were in the state of insulin-dependent diabetes. Twenty-three patients had normal glucose metabolism (Table 2). In terms of exocrine function, a normal pancreolauryl test was observed in 24% of the patients with CP and in 4 of the 6 patients with rAP.

Late Follow-up

All patients were followed in the outpatient clinic postoperatively. Ninety-six percent of the patients were followed closely. Four patients died in the follow-up period due to esophageal cancer (2), cardiac arrest (1), and suicide (1). One patient from Turkey was lost after a close follow-up of 2.5 years. The follow-up rate was 100%; the median length of the late follow-up was 39.3 months (range: 5–109 months). The data presented for the late follow-up period are based on the recent evaluation using the case history, the data from the exocrine and endocrine function tests, and the pain status measured by the VAS pain score.

Statistics

Statistical evaluation was performed using the McNemar and the Wilcoxon test. A P value <0.05 was considered significant.

RESULTS

DPPHR was performed in all 36 patients using the technique described elsewhere.[18,19] The wet weight of the operative specimens was between 25 and 45 g.

Table 2. Endocrine status

Patient condition	Preoperative (n = 36)	Early postoperative (n = 36)	Late postoperative* (n = 32)
Normal OGTT	23 (64%)	27 (75%)	24 (75%)
Impaired OGTT	11 (31%)	5 (14%)	3 (9%)
IDDM	2 (6%)	4 (11%)	5 (16%)

OGTT = oral glucose tolerance test; IDDM = insulin-dependent diabetes mellitus.
*Late postoperative follow-up: 32/32 patients (median follow-up: 39.3 months [range, 5–109 months]).

In one patient with a large pseudocyst of the pancreatic head, a pseudocyst drainage was performed. In two patients with a stenosis of the prepapillary common bile duct, caused by an inflammatory mass in the pancreatic head, internal biliary drainage, as described elsewhere, had to be performed.[18,19] In two additional patients with severe CP and dilated pancreatic main duct with multiple stenosis, a latero-lateral pancreaticojejunostomy using the Partington-Rochelle procedure was added to the DPPHR.[19]

Early Postoperative Course

The mean postoperative hospitalization period was 14.9 days. Early postoperative morbidity occurred in nine patients; we observed pleural effusions (two patients), pulmonary infection (two patients), cholangitis (one patient), transient ischemic attack (one patient), and gastrointestinal motility disorder and wound infection (one patient); one patient in the CP group had to undergo reoperation because of an intraabdominal abscess. Hospital mortality was 0% (Table 3). Concerning endocrine function, as assessed by the OGTT, 4 patients with preoperatively impaired glucose tolerance returned to normal status, whereas 2 additional patients developed insulin-dependent diabetes (Table 2). In terms of exocrine function, 25 patients with CP and 1 patient with rAP received substitute pancreatic enzymes because of ongoing exocrine functional impairment.

Late Postoperative Status

The follow-up period of the 36 patients was a median of 39.3 months (range, 5–109 months). Four patients died in the late follow-up period (one from suicide, one from cardiac arrest, and two from cancer of the esophagus), the late mortality being 11%. Five of 26 patients with CP and 1 of 6 with rAP were rehospitalized because of periods of pancreatitis. Two patients needed a reoperation; one patient had a stenosis of the pancreatic main duct anastomosis and one patient needed an additional duct drainage

Table 3. Early and postoperative results after DPPHR

Patient condition	CP (n = 30)	rAP (n = 6)	Total (n = 36)
Postoperative hospitalization (d)	14.8	15.5	14.9
Early postoperative morbidity	7	2	9 (25%)
Reoperation	1	0	1 (3%)
Hospital mortality	0	0	0 (0%)

CP = chronic pancreatitis; rAP = recurrent acute pancreatitis; DPPHR = duodenum-preserving pancreatic head resection.

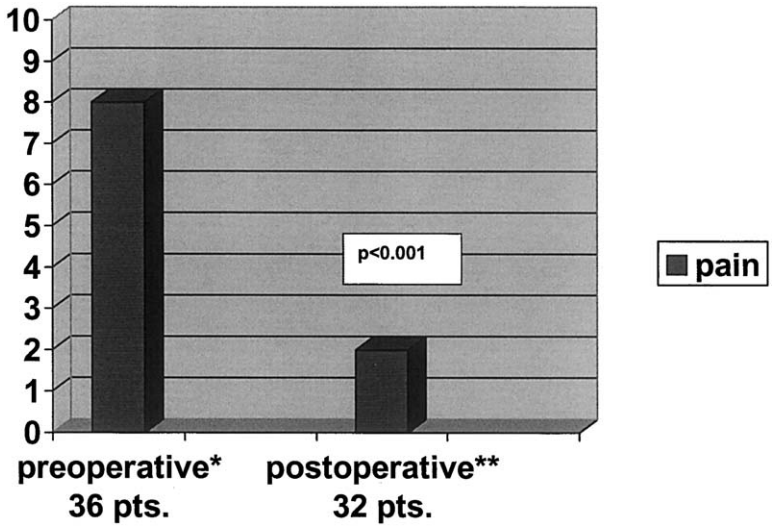

Fig. 1. Pain score before and after surgery. *May 1982 to February 2000, Department of General Surgery, University of Ulm, Germany. **Late postoperative follow-up: 32/32 patients (median follow-up: 39.3 months [range, 5–109 months]).

procedure because of the development of multiple pancreatic main duct stenosis and dilatations.

In terms of pain status, 16 (of 32) patients were completely pain-free in the long-term follow-up. The VAS pain score decreased significantly from a preoperative level of 8 points to a lower median level of 2 points ($P < 0.001$) (Fig. 1). Six (of 32) patients had further attacks of acute pancreatitis. The frequency of periods of hospitalization for pancreatitis dropped preoperatively from 1.8 per patient to 0.2 per patient ($P < 0.002$) (Table 4). In terms of endocrine status, 24 (of 32) patients remained in a normal glucose status. Eight (of 32) patients showed an impaired glucose status: 3 had an impaired OGTT and 5 had insulin-dependent diabetes mellitus (Table 2).

Table 4. Pain status after surgery

Patient condition	**Preoperative (n = 36)**	Late postoperative* (n = **32**)
Pain status		
Daily	14 (38%)	3 (9%)
Weekly	7 (19%)	2 (6%)
Monthly	14 (38%)	11 (34%)
No pain	1 (3%)	16 (50%)†
Pancreatitis attacks	35 (97%)	6 (19%)†
Periods of hospitalization	63 (1.8/pt)	6 (0.2/pt)†

*Late postoperative follow-up: 32/32 patients (median follow-up: 39.3 months [range, 5–109 months]).
†$P < 0.002$ (McNemar) preoperative vs. postoperative.

DISCUSSION

The appropriate treatment of PD depends on the severity of the clinical symptoms, the degree of alterations in the main duct and side branches, the state of the disease as shown by pathomorphological changes, and endocrine and exocrine function. The established medical treatment is not causally effective, but patients with minimal symptoms benefit from it.[8]

The clinical presentation of patients suffering from PD is characterized by the development of pancreatitis. In some patients, the obstruction of the pancreatic duct leads to rAP or finally to CP. However, PD might not be the only cause of pancreatitis in all patients. In our group of patients with PD, 9 patients reported alcohol consumption in their clinical history. In the group of patients with CP (30 patients), 8 patients had a history of light or moderate drinking of alcohol. Alcohol might have been a cofactor for the development of chronic pancreatitis in this group. On the other hand, only 1 of the 6 patients in the rAP group admitted alcohol consumption. Two patients (children) in the rAP group had never been exposed to alcoholic beverages.

A variety of interventional and surgical procedures have been used to reduce the degree of narrowing of the minor papilla and/or to bridge the narrowed segment of the duct of Santorini. Endoscopic dilatation or papillotomy of the minor papilla are mostly of limited benefit in respect to short-term pain relief and also bear the risks of local complications such as bleeding, pancreatitis, and ductal disruption.[22–24] Pain relief is frequently observed with endoscopic

stenting of the minor papilla; however, this procedure necessitates a change of the stents every 3 to 4 months.[25,26] The reported long-term results suggest a limited benefit in less than 50% of the patients with CP[27,28] and in 60% to 70% of patients with rAP.[29,30] Transduodenal surgical sphincteroplasty has been performed with a very low morbidity and, in relation to endoscopic sphincterotomy, a comparable mortality.[29,30] It had been performed in 30% of the patients in this series with a limited benefit. Five patients underwent stenting, with short-term benefit. In patients with a dilated duct system in the left pancreas a drainage procedure may be indicated, using a modification of the Partington-Rochelle procedure. Three patients of this series had a previous duct drainage that ultimately failed in terms of prevention of pain and further attacks of pancreatitis.

The pathomorphological changes of PD develop in the duct system in the pancreatic head. On the basis of CT investigations, 42% of the patients in our series demonstrated an inflammatory mass in the head of the pancreas. The presence of pseudocystic lesions in 28% of the patients and prepapillary stenosis of the duct of Santorini in 44% emphasized that the pancreatic head is the leading area in this type of CP and rAP. We decided on the basis of the beneficial experience with the DPHHR in patients with alcoholic CP to start a prospective investigation using DPPHR in patients with symptomatic PD.[18,19]

The major advantage of DPPHR in comparison to other resective procedures is the preservation of the gastrointestinal tract despite the removal of all of the pancreatic head except a shell-like remnant between the common bile duct and duodenal wall. This limited surgical resection has a low postoperative morbidity, and no hospital deaths occurred in this series of 36 patients. The surgical procedure can be combined with a drainage procedure of the dilated left pancreatic main duct, as was done in two patients. In patients with compression of the intrapancreatic common bile duct, it is easy to decompress the common bile duct or to perform a biliary anastomosis with the jejunal loop.

As demonstrated by the early and late postoperative evaluation of the endocrine function of the 36 patients, a nonsignificant improvement in the frequency of impaired glucose metabolism was seen in the early postoperative period; four patients with preoperatively impaired glucose metabolism had a more normal glucose tolerance postoperatively. Two patients showed a deteriorated endocrine function and went from impaired to insulin-dependent glucose metabolism. Nevertheless, there was an early postoperative improvement in 11% of the patients. This can be best explained by the importance of the duodenum for the preservation of the enteroinsulinar axis in glucose homeostasis (Table 2). After a median of 39.9 months of follow-up, 75% of the patients continued to demonstrate a normal glucose metabolism. However, three patients showed a deterioration in endocrine function and developed insulin-dependent diabetes mellitus.

In terms of pain status, 50% of the patients were completely pain-free in the late postoperative period, and 31% had a significant reduction of pain, shown by a reduction in the median VAS pain score from 8 to 2 (Fig. 1). Only 6 of the 32 patients experienced further attacks of pancreatitis, and the hospitalization rate was significantly reduced to 0.2 times per patient. Sixteen (50%) were not completely pain-free in the long-term follow-up (Table 4); however, only three (9%) suffered from continuing daily pain. Although a relatively high number of patients suffered from pain in the late postoperative period, only 13% (4/32) needed analgesic treatment regularly. The reduction in severity of pain can also be seen in the significant reduction of pain measured by the VAS pain score (Fig. 1).

These data show that the clinical symptoms of the disease in both groups of patients are improved by this surgical procedure. These favorable results were paralleled by improvement in the body weight in 90% of the patients. However, enzyme supplementation was mandatory in most of the patients because of the still reduced exocrine function capacity in the late postoperative period.

In PD causing rAP or CP an appropriate selection of treatment modalities, including interventional endoscopic treatment, is fundamental to transform the improvement of treatment modalities to the patients' long-lasting benefit. The first choice for treatment in patients with PD and a stenotic minor papilla should be endoscopic papillotomy. In patients with a stenotic segment of the d. Santorini in the pancreatic head, stenting of the duct should be the first approach. After failure of medical and interventional endoscopic treatment of PD causing rAP or CP, DPPHR offers major advantages in terms of preservation of the endocrine function and improvement in pain, resulting in a slower progression of the disease. This may be particularly important for the group of mostly young patients suffering from rAP. However, the observation time, with a median of 39.3 months (ranging up to 105 months), in this study was not sufficient to predict a long-lasting change in the natural course of the disease.

CONCLUSION

Upper abdominal pain and pancreatitis attacks are the leading symptoms of patients suffering from pancreas divisum. DPPHR represents a more physiologic

operation compared to pylorus-preserving duodenopancreatectomy in patients with pancreas divisum and chronic pancreatitis as well as recurrent acute pancreatitis. The limited resection of the pancreatic head with preservation of the duodenum led to a significant reduction of pain in 31% of patients. Fifty percent of the patients became completely pain-free. DPPHR furthermore preserves the endocrine function in the early and late postoperative period. The low recurrence rate of acute pancreatitis after DPPHR and the preservation of endocrine function may indicate a slower progression of the disease. The duodenum-preserving head resection has a low early and late morbidity and surgical-related mortality. The DPPHR offers a surgical option that promises a favorable short-term and beneficial long-term outcome after failure of interventional treatment of PD.

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Transphrenic Fistulization of a Subphrenic Abscess to Lung Parenchyma

Sander Romijn, M.D., Maarten Sturm, M.D., Georges van der Schelling, M.D.

A 53-year-old woman was admitted with respiratory distress. For several years, she had chronic alcoholic pancreatitis with ductal stones that were treated with a stent and with shockwave lithotripsy. Both treatments were unsuccessful, and the pancreatitis was complicated with an infected pseudocyst. The pancreatic head had to be resected, which was complicated with recurrent subphrenic abscesses. She then was admitted with respiratory distress and initially diagnosed with pneumonia of the right lower lobe. Further investigations showed supradiaphragmatic and subdiaphragmatic air-fluid levels. In both collections *Streptococcus milleri* was cultured, and subsequently the patient was diagnosed with a fistula connecting the subdiaphragmatic abscess with pulmonary tissue. This was treated with intravenous amoxicillin/clavulanate and drainage of the subdiaphragmatic collection. She did not develop a pulmonary empyema, because multiple adhesions, which were due to recurrent abscesses after pancreatic surgery, prevented breakthrough into the pleural cavity. (J GASTROINTEST SURG 2005;9:716–717)

KEY WORDS: Pancreatitis, pancreatic surgery, subphrenic abscess, fistula

Intra-abdominal inflammation can cause enteroenteral fistulas, as seen in Crohn's disease. Intrathoracic inflammation can result in bronchopleural fistulas, as seen in pneumonic abscesses. Our patient presented with an abdominothoracic fistula due to a subphrenic abscess, a complication after pancreatic surgery.

CASE REPORT

A 53-year-old woman presented with respiratory distress. She was known to have chronic pancreatitis caused by excessive alcohol consumption. For several months, she had complained of progressive abdominal pain, intermittent vomiting, and anorexia. An abdominal computed tomography (CT) scan showed concrements in the pancreatic duct and signs of chronic calcifying pancreatitis. An endoscopic retrograde cholangiopancreaticogram was performed, and a prepapillary stricture with a widened pancreatic duct was seen. The pancreatic duct contained stones. The stricture was treated with a stent. This treatment, however, was unsuccessful, and because of persistent complaints, the patient was transferred to a university hospital. Here, she underwent extracorporeal shockwave lithotripsy to pulverize the pancreatic stones. At 5 weeks later, ongoing abdominal pain made readmission necessary. An abdominal CT showed a fluid collection near the pancreas suspicious for a pseudocyst. Puncture and analysis of this collection cultured *Escherichia coli*, and the diagnosis of an infected pseudocyst was made. This was treated with drainage, and to prevent recurrence, she underwent surgical removal of the pseudocyst and the pancreatic head according to Beger's method.[1] The surgical procedure was complicated with a persistent subphrenic abscess, which was repetitively treated with percutaneous drainage. She was referred by the general practitioner to our hospital for continuing respiratory distress. She had difficulty breathing, had no appetite, was nauseated, and vomited mucus. She also had abdominal pain caused by her chronic pancreatitis. Physical examination showed a weak, cachectic, ill woman with dyspnea. There was no jaundice or anemia. She had a fever with a temperature of 38.6°C.

Her blood pressure was 177/100 mm Hg, and her heart rate was 105/min. Pulmonary examination demonstrated rhonchi in both lung fields and diminished breath sounds, particularly in the right lower lung field. Increased tactile and vocal fremitus and dull

From the Departments of Surgery (S.R., G.v.d.S.) and Radiology (M.S.), Amphia Hospital, Breda, the Netherlands.
Reprint requests: Sander Romijn, M.D., Langendijk 75, 4819 EV, Breda, the Netherlands. e-mail: sanderromijn@chello.nl

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percussion were present in the right lower lung field. Abdominal examination revealed tenderness in the epigastric region. Laboratory findings showed a leukocyte count of 44.8×10^9/L (reference, 4.0–10.5×10^9/L) and an abnormal gas exchange (P_{CO_2}, 9.5 kPa [reference, 4.5–6.1 kPa]; P_{O_2}, 8.2 kPa [reference, 10.6–13.3 kPa]). On chest radiograph, alveolar consolidation was seen in the right lower lobe. Based on these findings, she was initially diagnosed with respiratory failure due to pneumonia of the right lower lobe. She was admitted to the intensive care unit for intubation, mechanical ventilation, and antimicrobial therapy with intravenous amoxicillin/clavulanate 2.2 g four time daily and tobramycin 5 mg/kg. A sputum sample was taken for culture. On day 2, an abdominal ultrasound showed a subphrenic fluid collection. This collection was punctured under ultrasound guidance, and purulent fluid was retrieved and cultured. A drain was left behind for irrigation and drainage. On day 3, chest and abdominal CT scans revealed supradiaphragmatic and subdiaphragmatic air-fluid levels (Fig. 1). Microbiological results proved the connection between the two cavities. In both samples, *Streptococcus milleri* was cultured. Based on these findings, she was diagnosed with a subphrenic abscess after pancreatic surgery with breakthrough through the diaphragm into the pulmonary parenchyma, without formation of empyema.

Further treatment consisted of intravenous amoxicillin/clavulanate 2.2 g four times daily and drainage, which resulted in day-by-day improvement.

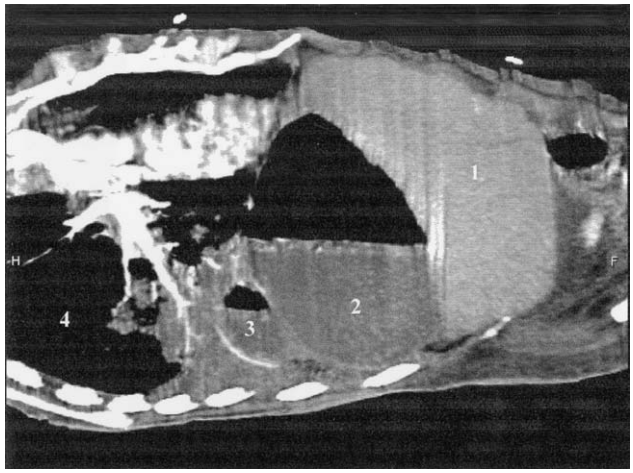

Fig. 1. The subphrenic abscess shifts the liver down. H = cephalad, F = caudad, 1 = liver, 2 = subphrenic abscess, 3 = pulmonary abscess, 4 = right lung.

DISCUSSION

Fistulous connections develop in inflammatory processes at a locus minoris resistentiae. Intra-abdominal inflammation can cause enteroenteral fistulas, and intrathoracic inflammation can result in bronchopleural fistulas, as seen in pneumonic abscesses. Our patient presented with an abdominothoracic fistula due to a subphrenic abscess, a complication after pancreatic surgery. The literature does not describe a fistulous connection between a subphrenic abscess and pulmonary tissue without formation of empyema. In our case, *S. milleri* was cultured, which is known for abscess formation. An empyema was probably not formed in our patient because her repetitive subphrenic abscesses resulted in pleural adhesions. Thus, the pleural cavity was no longer a locus minoris resistentiae.

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Survival After Gastric Adenocarcinoma Resection: Eighteen-Year Experience at a Single Institution

Steven C. Cunningham, M.D., Farin Kamangar, M.D., M.P.H., Min P. Kim, M.D., Sommer Hammoud, Raqeeb Haque, Anirban Maitra, M.B.B.S., Elizabeth Montgomery, M.D., Richard E. Heitmiller, M.D., F.A.C.S., Michael A. Choti, M.D., F.A.C.S., Keith D. Lillemoe, M.D., F.A.C.S., John L. Cameron, M.D., F.A.C.S., F.R.C.S.(Eng.) (hon), F.R.C.S.I. (hon), Charles J. Yeo, M.D., F.A.C.S., Richard D. Schulick, M.D., F.A.C.S.

Gastric adenocarcinoma is the second leading cause of cancer death worldwide. In Western series, survival rates vary widely and are generally lower than those reported from Eastern series. We performed a retrospective analysis of cases operated on at the Johns Hopkins Hospital over the past 18 years and collected data on demographics, tumor characteristics, pathologic stage, treatment methods, complications, survival time, and other relevant factors. Survival according to stage of disease, Lauren tumor type, tumor location, time period, and administration of adjuvant therapy was analyzed, and results were compared with those of other Western series. During this period, 436 patients with gastric adenocarcinoma underwent resection. We have shown a statistically significant association between survival and margin status, stage of disease, and Lauren tumor type. Overall 5-year survival was 26%, and 5-year survival after R0 resection was 33%. No significant difference was detected between survival and tumor location, time period of treatment, or administration of adjuvant therapy. Analysis of various Western series reveals major differences between the cohorts under study, such as stage of disease, extent of resection, tumor type, and tumor location. Many of the reported differences among Western series may be due to cohort differences, such as stage of disease, extent of resection, tumor type, and tumor location. (J GASTROINTEST SURG 2005;9:718–725)

KEY WORDS: Stomach neoplasms, adenocarcinoma, mortality, survival

Gastric adenocarcinoma (GA) is the second leading cause of cancer death worldwide.[1] There are an estimated 22,710 new cases of gastric cancer annually in the United States, and about 11,780 of those patients will die of their disease.[2] Over the past several decades, the epidemiologic profile of gastric cancer has changed dramatically. Although the incidence of gastric noncardia adenocarcinoma (GNA) is decreasing, the incidence of gastric cardia adenocarcinoma (GCA) is increasing.[3]

Survival after resection of GA has been studied in multiple series with patients stratified by stage of disease, Lauren tumor type,[4] tumor location, time period, and administration of adjuvant therapy. All studies uniformly show an association between stage and survival. The Lauren classification correlates significantly with survival, in that intestinal-type tumors are associated with longer survival than are diffuse-type tumors.[5] According to some data analyses, tumor location is significantly associated with survival, with GNA having an improved prognosis over GCA.[3] In many studies, both operative mortality and 5-year survival have improved over the past several decades.[6–8] With respect to adjuvant therapy, MacDonald et al.,[9] in a randomized controlled clinical trial, showed an improvement in survival with adjuvant chemoradiotherapy.

From the Departments of Oncology (S.C.C., M.A.C., C.J.Y., R.D.S.), Pathology (A.M., E.M.), and Surgery (R.E.H., M.A.C., K.D.L., J.L.C., C.J.Y., R.D.S.) and the Curriculum in Medicine (M.P.K., S.H., R.H.), The Johns Hopkins University School of Medicine, and the Department of Epidemiology (F.K.), the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and the Department of Surgery, University of Maryland Medical Center (S.C.C.), Baltimore, Maryland.

Reprint requests: Richard D. Schulick, M.D., F.A.C.S., Department of Surgery, Room 442, Cancer Research Building, 1650 Orleans Street, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD 21231-1000. e-mail: rschulick@jhmi.edu

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In light of these separate survival findings, we examined survival as a function of all of the above factors in our 18-year single-institution experience. In addition to survival data, we assessed patient, tumor, and operative characteristics for this cohort.

PATIENTS AND METHODS

From May 1984 through July 2002, 436 patients with GA underwent resection at the Johns Hopkins Hospital. Under Johns Hopkins University Institutional Review Board-approved exemption 45 CFR 46.101(b), demographic characteristics, date of surgery, presenting signs and symptoms, stage, surgical and medical treatment methods, complications, survival time, and other relevant data were extracted from hospital records. Patient confidentiality was ensured in all cases.

Staging data are provided according to the sixth edition of the American Joint Committee on Cancer's *Cancer Staging Manual*.[10] For the purpose of this study, *morbidity* was defined as a complication, that is, a disease or disorder that occurred as a result of GA or its resection, and *operative mortality* was defined as death occurring during or within 30 days of the operation.

The Kaplan-Meier method was used to calculate survival.[11] Survival rates were compared using log-rank tests and Cox proportional hazards models. In bivariate analyses, the results of log-rank test and Cox model were almost identical; therefore, only results from the Cox model are reported. Cox proportional hazards model was also used to test the significance between survival after adjustment for age and stage. The assumption of proportionality of hazards was verified in all tests. For comparisons of early versus late study periods, the early period was May 16, 1984, through January 1, 1995 (N = 198), and the late period was January 2, 1995, through July 24, 2002 (N = 233). Significance was accepted at $P < 0.05$.

RESULTS

Patient Characteristics

The median age of the patients at the time of diagnosis was 66 years. Patients were predominantly white men: 305 (70%) were males, 314 (72%) were white, 80 (18%) were black, and 42 (10%) were of other descent. The most commonly reported comorbid conditions were hypertension (33%), gastroesophageal reflux (14%), peptic ulcer disease (13%), and diabetes mellitus (10%). Pain (33%), weight loss (32%), and dysphagia (26%) were the most common presenting symptoms. There was no significant change in age at diagnosis ($P = 0.73$) or gender ($P = 0.45$) between the early and late periods of the study.

Tumor Characteristics

Patient and tumor characteristics are shown in Table 1. The most common tumor location was the cardia in 160 (37%) patients, followed by the antrum in 86 (20%), the body in 22 (5%), the fundus in 19 (4%), the pylorus in 12 (3%), and multiple or overlapping locations in 137 (31%). In this series, the cardia was a significantly more common location during the late time period than during the early period (53% versus 31%, respectively; $P < 0.001$). Tumor stage at diagnosis was stage I in 85 (20%), stage II in 83 (19%), stage III in 145 (34%), and stage IV in 117 (27%) (Fig. 1).

Histologic evaluation was available for all the resected specimens. In only 224 cases were data regarding cell morphology present in the final pathology report. The majority (160; 71%) were diffuse type with signet cell morphology, and 64 (29%) were intestinal-type cancers.

Treatment Characteristics

Operative Treatment. The most common operations were subtotal distal gastrectomy (36%), proximal resections (proximal gastrectomy with or without transhiatal esophagectomy [THE]) (34%), and total gastrectomy (29%); accordingly, the usual reconstruction techniques were gastrojejunostomy, esophagogastrostomy, and esophagojejunostomy, respectively. Of 373 patients with unambiguous data available regarding tumor margins, 109 (29%) had positive margins reported in the final pathology

Table 1. Patient and Tumor Characteristics

Median patient age (yr)	66
Male gender (n)	305 (70%)
Female gender (n)	131 (30%)
Tumor stage (n)	
I	85 (20%)
II	83 (19%)
III	145 (34%)
IV	117 (27%)
Tumor location (n)	
GCA	160 (37%)
GNA	276 (63%)
Tumor type (n)	
Intestinal	64 (29%)
Diffuse	160 (71%)

GCA = gastric cardia adenocarcinoma; GNA = gastric noncardia adenocarcinoma.

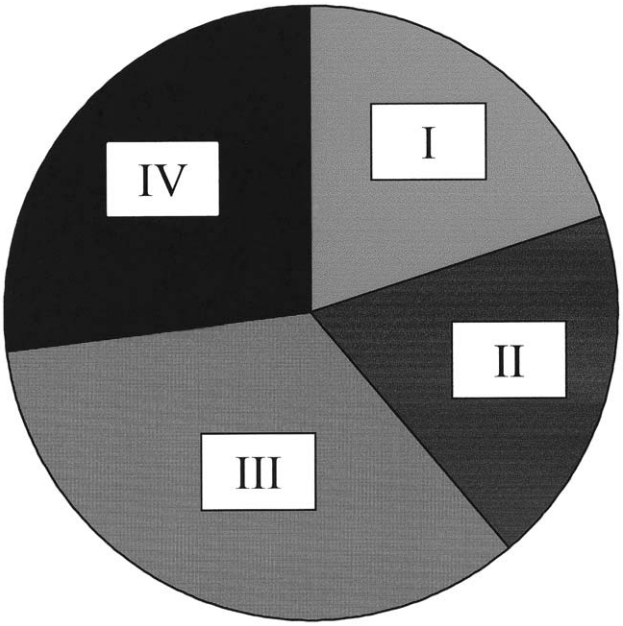

Fig. 1. Tumor stage at diagnosis for 430 patients. The majority of patients had advanced disease at the time of resection: stage I, 85 (20%); stage II, 83 (19%); stage III, 145 (34%); stage IV, 117 (27%).

report. Proximal gastrectomy plus THE was a significantly more likely operation during the late time period than during the early period ($P < 0.001$), whereas there was a significant decline in the use of subtotal distal and total gastrectomies ($P < 0.001$) in the late period compared with the early period. Regarding lymphadenectomy, the standard practice at our institution over the past two decades has been a D1 dissection, that is, removal of the nodes in Group 1 of the Japanese Classification of Gastric Carcinoma (the perigastric lymph nodes). This is the most common procedure performed in the United States and Europe[12,13] and has recently been shown in a randomized clinical trial to result in significantly less morbidity and equal survival at long-term (11-year) follow-up compared with the more extensive D2 operation.[14]

Adjuvant Treatment. One hundred twenty-two patients received postoperative adjuvant, and 41 received neoadjuvant therapy. Adjuvant regimens were highly varied over the 18 years spanned by this series. Neoadjuvant therapy was significantly more likely to be administered during the late time period than during the early period (15% versus 7%, respectively; $P < 0.02$).

Morbidity and Mortality

Data regarding complications were available for 335 of the 436 patients in the study. The eight most common complications and their occurrence, respectively, were anastomotic leak, 15 of 335 (4%); pneumonia, 15 of 335 (4%); arrhythmia, 14 of 335 (4%); wound infection, 13 of 335 (4%); ileus, 11 of 335 (3%); postoperative fever of uncertain origin, 11 of 335 (3%); psychiatric complications, 9 of 335 (3%); and urinary tract infection, 7 of 335 (2%). Other complications and their occurrence, respectively, were intra-abdominal infection, 4 of 335 (1%); intestinal obstruction, 3 of 335 (1%); cardiac arrest, 3 of 335 (1%); bacteremia, 3 of 335 (1%); central venous catheter-related infections, 2 of 335 (<1%); pleural effusion, 2 of 335 (<1%); marginal ulcer, 2 of 335 (<1%); pancreatitis, 1 of 335 (<1%); and myocardial infarction, 1 of 335 (<1%). Reoperation was required in 10 of 335 (3%) patients. Operative death occurred in 11 of 433 (2%) patients. The complication and operative mortality rates in the early and late periods of the study were not significantly different ($P = 0.69$).

Survival

Five-year survival was calculated for the study population stratified by tumor stage (I versus II versus III versus IV), margin status (R0 versus R1/2), Lauren type (diffuse versus intestinal), tumor location (GCA versus GNA), time period of treatment (1984–1994 versus 1995–2002), and administration of adjuvant therapy (Table 2). Survival correlated significantly with stage of disease (Fig. 2), positive margin status (Fig. 3), and with Lauren tumor histology type (Fig. 4). Five-year survival in patients operated on during the early time period was 23% compared with 31% for the late period, a difference that did not reach statistical significance. No significant association was detected between survival and tumor location or adjuvant therapy in this retrospective analysis.

DISCUSSION

Survival after resection of GA has improved over the past half-century.[7] Still, each year more than half of those individuals who acquire GA die of the disease in the Western world.[2] Stage-stratified survival appears to be much higher in the Eastern than in the Western world.[15–18] Three hypotheses explaining this difference were previously reviewed.[19] First, the "different disease" hypothesis invokes race-related differences in tumor biology or tumor–host interaction. Second, the "stage migration" or "Will Rogers phenomenon" hypothesis holds that improved detection of disease due to more extensive lymphadenectomy and lymph node analysis results in an upstaging of disease such that the survival of each

Table 2. Survival

Parameter	N (in survival analysis)	5-Year Survival (%)	Unadjusted Hazard Ratio (*P* value)*†	Adjusted Hazard Ratio (*P* value)*‡
Stage				
I	85	63		
II	81	28		
III	144	18	1.74 (<0.001)	1.78 (<0.001)
IV	115	10		
All	425	26		
Margin status				
R0	264	33	2.50 (<0.0001)	1.88 (<0.0001)
R1/2	109	10		
Tumor type				
Diffuse	158	20	1.76 (0.005)	1.57 (0.03)
Intestinal	62	36		
Tumor location				
GCA	160	28	0.92 (0.54)	0.86 (0.29)
GNA	206	29		
Time period				
1984–1994	198	23	0.84 (0.15)	0.88 (0.32)
1995–2002	233	31		
Adjuvant therapy				
Yes	150	20	1.18 (0.23)	0.86 (0.30)
No	204	27		

GCA = gastric cardia adenocarcinoma; GNA = gastric noncardia adenocarcinoma.
*Hazard ratios are calculated for each level of increment in stage, R0 versus R1/2 margin status, diffuse versus intestinal, GNA versus GCA, early versus late period, and positive versus negative history of either adjuvant or neoadjuvant therapy.
†Unadjusted *P* values are calculated using Cox proportional hazards model.
‡Adjusted *P* values are derived from Cox proportional hazards model after adjustment for age and stage.

stage group increases. Last, according to the "treatment" hypothesis, the more extensive lymph node dissections favored by the Japanese generate a superior therapeutic response. It may be that all three hypotheses contribute in some manner to explaining the Western–Eastern difference. The following discussion applies predominantly to Western series of GA.

In this study, we compared survival rates of patients with resected GA after stratification by stage, Lauren tumor type, location, time period, and use of adjuvant therapy. Our results largely agree with the previously reported Western experience. Comparison across studies, however, is wrought with difficulty due to time- and institution-dependent differences in staging, treatment biases, and referral patterns. In the present study, we evaluated survival by each of the above parameters within the same cohort.

Overall survival after resection of GA varies widely in the literature (Table 3), ranging from a relative 5-year survival of 20% according to 1990 SEER data,[1] to 28% according to National Cancer Data Base data,[19] to 32%–49% according to the two largest published Western single-institution series,[20,21] to 65% in a large Eastern series.[18]

Consistent with published data, we found a significant relationship between stage and survival. Nearly all series of GA provide stage-stratified data, but some studies include only R0 resections, whereas other studies include all resections (Table 3). As expected, those studies that do not eliminate R1 and R2 cases (the present study included) tend to have lower overall survival than those studies including only R0 resections.

With respect to the Lauren classification of tumor type, we found that the survival of patients with diffuse-type histology was significantly lower than that of patients with intestinal-type histology. This is consistent with published studies that do not exclude gastroesophageal junction (GEJ) tumors from the analysis,[22] an important consideration because tumors in the GEJ are more likely to be of the diffuse-type histology with a correspondingly poorer prognosis.

Regarding the association between tumor location and survival, conflicting data exist. Studies that eliminate GEJ tumors, for example, find no significant association between survival and tumor location.[22,23] Other studies that included GEJ tumors in the analysis, however, have found that distal tumors are associated with an improved prognosis compared with

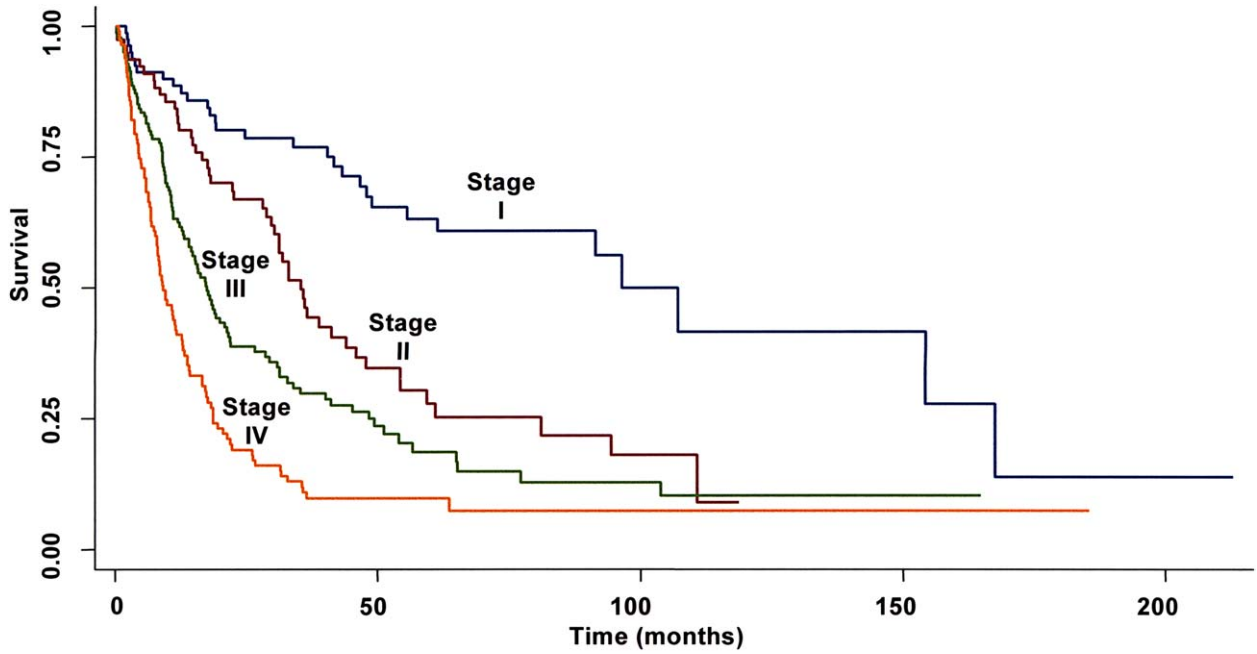

Fig. 2. Kaplan-Meier survival graph for 430 patients stratified by stage of disease after resection of gastric adenocarcinoma. The 5-year survival rates by stage of disease were 63% for stage I, 28% for stage II, 18% for stage III, and 10% for stage IV ($P < 0.001$).

proximal tumors.[3,24–27] Here, we found no significant association between proximal and distal lesions, likely due to the much larger proportion of patients in our study with more advanced disease. For example, in one study examining proximal versus distal GA, Harrison et al.[24] reported a 42% 5-year survival rate for proximal GA and a 61% 5-year survival rate for distal lesions. However, only 43% of patients in that study had stage III or IV disease, whereas in our study the proportion is over 60%. Furthermore, our study has included approximately 10-fold as many patients with stage IV disease.

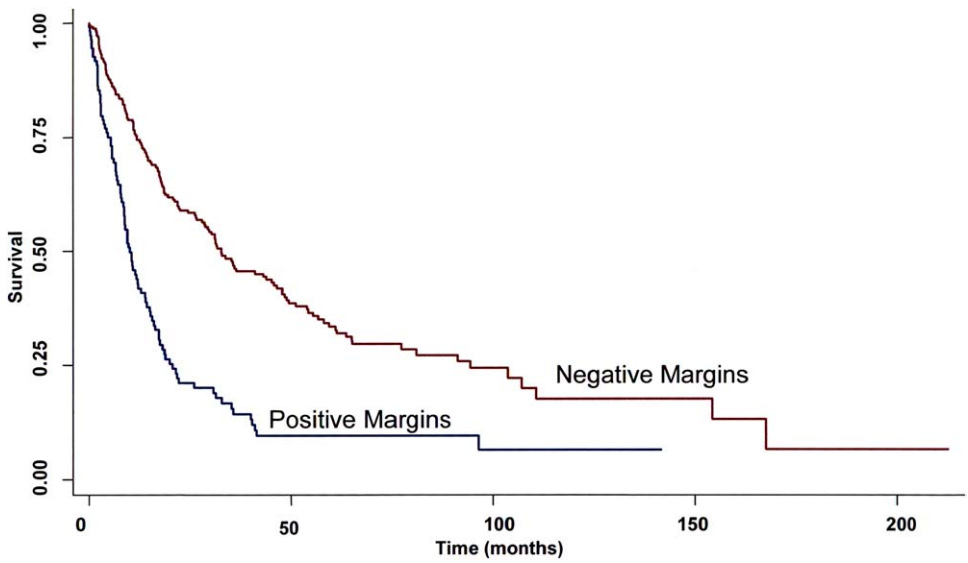

Fig. 3. Kaplan-Meier survival graph for 373 patients stratified by status of margin of resection on final pathologic diagnosis. The 5-year survival rates by margin status were 33% for margin-negative resections and 10% for margin-positive resection ($P < 0.0001$).

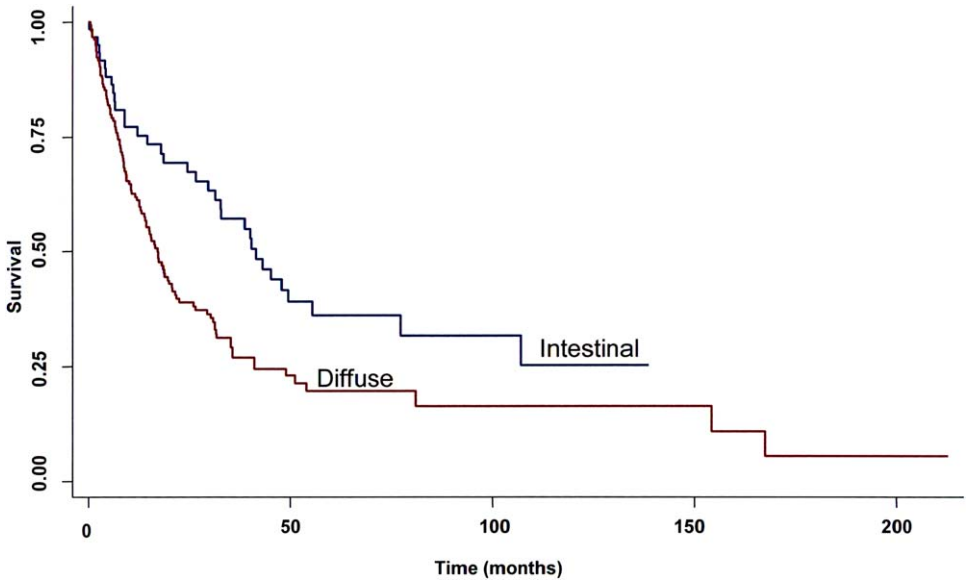

Fig. 4. Kaplan-Meier survival graph for 224 patients stratified for Lauren histology type after resection of gastric adenocarcinoma. The 5-year survival rates by histology type were 36% for intestinal histology and 20% for diffuse histology ($P = 0.03$).

Similarly, with respect to overall 5-year survival, patient cohort differences provide explanations for the lower overall survival compared with other Western series. Karpeh et al.,[21] for example, reported an overall 5-year survival rate after R0 resection or GA to be 49%. However, there are at least three major differences between that cohort and our cohort: (1) again, in that study, as in Harrison et al., there were more patients with lower-stage disease than in the present study; (2) only patients with an R0 resection were included in the Karpeh et al. series, whereas R0, R1, and R2 were included in our series; and (3) in an earlier report from these investigators reporting tumor location,[24] there were 3.4-fold as many patients with distal tumors as proximal tumors, compared with only 1.7-fold in the current series. Although our series did not bear out a survival difference between proximal and distal location, multiple studies have indicated that proximal location is associated with a worse survival (Table 3). Furthermore, although Karpeh et al. do not report the proportion of patients with diffuse versus intestinal histology, our series has nearly twofold as many patients as those series that do report this proportion (Table 3).

In a large meta-analysis of 100 English-language publications since 1970, Akoh and Macintyre[7] found survival to improve from early to later time periods. In the current study, we found only a nonsignificant difference. This is likely due to the limited sample size imposed by a single-institution study, the advanced disease that characterized our tertiary-care population, the shorter and more recent time period spanned by our series, and the greater proportion of cardia tumors during the late period compared with the early period (53% versus 31%, respectively; $P < 0.001$).

In 2001, MacDonald et al.[9] showed, in a prospective randomized clinical trial (RCT) of adjuvant treatment, a significant improvement in survival following GA resection, but grade 3 toxicity occurred in the majority of patients. In an effort to improve the toxicity profile of effective adjuvant chemoradiation, another group recently studied an alternative chemoradiation regimen and found the rate of grade 3 toxicity to decrease to 38%, but due to small sample size (N = 18 postoperative patients) and short follow-up (1 year), the effectiveness of this less-toxic regimen in unclear.[28] Other recent RCTs of chemotherapy without radiation have failed to show a difference.[29,30] A recent multi-institutional trial of preoperative chemoradiotherapy suggested that neoadjuvant therapy may add meaningful survival time to the now standard adjuvant therapy.[31] However, this study contained only 34 patients and was performed in nonrandomized fashion. To fully evaluate this issue, larger RCTs must be performed. In our retrospective study, we observed no significant improvement in survival with adjuvant therapy, likely due to the lack of a uniform regimen over the study's 18-year period.

The limitations of our study include its retrospective nature, which precludes the controlled acquisition and real-time verification of data that benefit prospective series.

Table 3. Review of Western Gastric Cancer Series During the Past Two Decades

First Author/Year	Institution or Country/ Reference	N/Time Period	5YS Overall (%)	5YS Only R0 (%)	5YS by Stage, All (I, II, III, IV) (%)	5YS by Stage, R0 only (I, II, III, IV) (%)	5YS by Location (%)		Proximal Location (%)	Diffuse Type (%)
							Proximal	Distal		
Akoh/1992	Meta-analysis/7	52,927/1980s only	28.4	55.4	NR	NR	NR	NR	NR	NR
Soreide/1996	Mayo Clinic/22	187/1978–1988	NR	48*	NR	78, 46, 20, NR*	NS*	NS*	10*	NR
Sanchez-Bueno/1998	Spain/23	297/1979–1994	39*	NR	85, 52, 23, 0*	NR	NS*	NS*	11*	NR
Pisani/1999	SEER/1	NR/1990 only	20	NR	NR	NR	NR	NR	NR	NR
Hundahl/2000	NCDB/19	50,169/1985–1996	28	NR	78/58, 34, 20/8, 7§	NR	20	34	28	NR
Karpeh/2000	MSKCC/21	1038/1985–1999	NR	49	NR	~90, 50, 25, 10	42†	61†	23†	NR
Piso/2000	Germany/27	532/1986–1997	NR	NR	NR	83, 52, 40, 11	25	47	53	NR
Jahne/2001	Germany/20	1114/1968–1998	32	37	95/75, 46, 26/11, 7§	NR	40	55	33	36
Talamonti/2003	NWU/25	110/1987–2001	NR	42	NR	62, 25‡	29	54	37	37
Present study/2004	JHMI	436/1984–2002	26	33	63, 28, 18, 10	65, 31, 26, 10	28	29	37	71

5YS = 5-year survival; NR = not reported; NS = not statistically significant; NCDN = National Cancer Database; SEER = Surveillance, Epidemiology, and End Results; MSKCC = Memorial Sloan-Kettering Cancer Center; JHMI = Johns Hopkins Medical Institutions; NWU = Northwestern University.

*Excluded patients with cardia tumors.

†From an earlier report of same series (reference 24).

‡T1-2, T3-4, respectively.

§Ia/Ib, II, IIIa/IIIb, IV.

CONCLUSION

We have shown a statistically significant association between survival after GA resection and margin status, stage of disease, and Lauren tumor type. No significant difference was detected between survival and tumor location, time period of treatment, or adjuvant therapy in this single-institution retrospective study. Series-specific patient selection and elimination differences, such as stage of disease, extent of resection, tumor type, and tumor location, may result in discordant survival rates between different series.

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Identification and Management of an Errant Antiperistaltic Roux Limb After Total Gastrectomy

John K. DiBaise, M.D., F.A.C.G., Kishore Iyer, M.B.B.S., F.R.C.S. (Eng.), F.A.C.S., Jon S. Thompson, M.D., F.A.C.S.

We recently evaluated two patients because of persistent, unexplained bilious vomiting following total gastrectomy with Roux-en-Y esophagojejunostomy. With the aid of intestinal manometry and reoperation, an antiperistaltic Roux limb was discovered in both cases. Isoperistaltic repositioning of the Roux limb led to resolution of both patients' symptoms. These case reports illustrate the devastating consequences of a poorly constructed Roux-en-Y esophagojejunostomy and demonstrate the utility of intestinal manometry in aiding the diagnosis of problems related to the Roux limb, particularly when surgical reexploration is not preferred or is inconclusive. By highlighting this avoidable technical error, we hope to prevent its future occurrence. (J GASTROINTEST SURG 2005;9:726–732)

KEY WORDS: Roux-en-Y, manometry, gastrectomy, juvenile polyposis, Ménétrier's disease

To err is human…
Alexander Pope, *An Essay on Criticism*, 1711

Roux-en-Y reconstruction is a well-established surgical option following gastric resection. We report on two patients we recently saw who were referred to our institution because of persistent bilious vomiting following total gastrectomy with Roux-en-Y esophagojejunostomy. These cases presented novel problems related to both diagnosis and management. At reoperation, an antiperistaltic Roux limb was suspected. Given the supporting evidence from preoperative intestinal manometry, which also suggested a Roux reversal, isoperistaltic repositioning was carried out and led to complete resolution of their symptoms. Although the reported complication appears to be extremely rare, the Roux-en-Y reconstruction is used routinely in modern surgery and our hope in presenting these cases is to highlight the devastating consequences of improper technique, to prevent future occurrence of this previously unreported complication.

CASE REPORTS

Case 1

A 51-year-old man with generalized juvenile polyposis (JP) syndrome was transferred to our institution 4 months postoperatively because of persistent, unexplained bilious vomiting following total gastrectomy and Roux-en-Y esophagojejunostomy performed because of chronic bleeding and protein-losing enteropathy related to extensive gastric polyposis. No evidence of malignancy was found in the gastrectomy specimen. He had been diagnosed with JP in 1998 and subsequently underwent a total proctocolectomy with ileostomy. His past medical history was otherwise notable for type 2 diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease. He had previously undergone a cholecystectomy.

His postoperative course was complicated by the immediate development of persistent bilious vomiting resulting in recurrent aspiration pneumonia. In addition, esophagojejunal anastomotic leakage developed on three separate occasions, requiring repeated surgical intervention. Evaluation performed locally did not demonstrate evidence of bowel obstruction, and he was unable to tolerate enteral feeding via a

From the Intestinal Rehabilitation Program, Departments of Internal Medicine (J.K.D.) and Surgery (K.I., J.S.T.), University of Nebraska Medical Center, Omaha, Nebraska.
Reprint requests: John K. DiBaise, M.D., Mayo Clinic Scottsdale, 13400 E, Shea Blvd., Scottsdale, AZ 85259. e-mail: dibaise.john@mayo.edu

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jejunostomy tube placed at the time of the gastrectomy. He subsequently had received parenteral nutrition. Placement of a nasoenteral tube into the Roux loop was noted to remove about 600–700 ml of bilious material daily.

Further history revealed that the vomiting was not preceded by nausea and occurred during the day and night. There was no abdominal discomfort or distention, and the ostomy functioned normally. Subsequent evaluation included an abdominal computed tomography scan that demonstrated a fluid-filled esophagus suggestive of anastomotic stenosis but no evidence of bowel obstruction or abscess. Upper endoscopy revealed LA classification Grade D esophagitis extending to his proximal esophagus and a high-grade anastomotic stricture that could not be traversed with a standard adult diagnostic videoendoscope. Following balloon dilatation of the stricture, the endoscope was advanced across the anastomosis. Within the Roux limb immediately distal to the esophagojejunal (EJ) anastomosis, a mucosal defect, thought to represent a fistulous opening, was seen. No other mucosal abnormalities were identified in the Roux limb. Antegrade and retrograde barium contrast studies through a nasojejunal tube and his ileostomy revealed no evidence of obstruction, bowel dilatation, or retrograde flow of contrast. Hepatobiliary scintigraphy did not detect clear evidence of a bilioenteric fistula, and no radionuclides were seen within the esophagus.

Due to continued suspicion of a bilioenteric fistula, the patient underwent an exploratory laparotomy, during which a long sinus tract extending from the esophageal anastomosis to the hilum of the liver was found and corrected. There was no evidence of obstruction. The Roux limb was noted to be very long, about 100 cm. Due to concern that this could be contributing to his persistent bilious vomiting, the Roux limb was shortened to 60 cm. Although a suspicion was raised as to whether the Roux limb was oriented in an antiperistaltic fashion, two experienced surgeons could not satisfactorily confirm this. In view of the more likely explanation for persistent biliary vomiting noted earlier, the orientation of the Roux loop was left unchanged.

Postoperatively, his bilious vomiting did not improve. In an attempt to differentiate between potential reversal of the Roux loop and severe Roux limb dysmotility, intestinal manometry using a six-sensor solid-state ambulatory system was performed. Visual analysis of the tracing revealed normal amplitude and frequency of contractile activity in the Roux limb, paucity of phase II activity, and frequent phase III activity, occurring about once per hour, with obvious disorganized motor activity and numerous abnormalities in propagation of the phase III, most notable for retrograde propagation in the vast majority (Fig. 1, *A*). There were no findings suggestive of mechanical obstruction.

With the additional supportive, albeit nonconfirmatory, evidence for inadvertent reversal of the Roux limb, a decision was made to reexplore the patient. Upon surgical exploration, it was thought that the mesentery of the distal bowel appeared to be completely separate from the mesentery to the Roux loop that was in continuity with the proximal jejunal mesentery (Fig. 2), findings consistent with a reversed Roux limb. Following extensive adhesiolysis, division of the Roux-en-Y esophagojejunostomy with placement in its proper isoperistaltic orientation was accomplished (Fig. 2, *C*). Resection of the previous Roux limb was specifically avoided, favoring instead to reorient it in an isoperistaltic fashion due to concern for remaining bowel length and potential problems related to high ostomy output if any additional bowel length was lost.

The patient's postoperative course was uneventful. The bilious vomiting resolved within 24 hours of the operation. He was discharged home 1 month postoperatively—7 months following the original gastrectomy—with combined oral and jejunostomy tube feeding. Over the following 2 years, he has done well: jejunostomy tube feedings ended over a year ago, he has regained his weight to his pregastrectomy level, and he empties his ostomy bag three or four times per day.

Case 2

More recently, a 39-year-old woman with Ménétrier's disease presented for evaluation of chronic vomiting and weight loss following total gastrectomy with Roux-en-Y esophagojejunostomy performed at another university medical center 3 months previously. She complained of bilious vomiting, up to 10 times a day, which was unrelated to eating and not preceded by nausea. This began immediately following her surgery. As a result, she had lost 40 pounds postoperatively. Abdominal pain was not a significant complaint. There was no evidence of malignancy in the gastrectomy specimen. Treatment with antisecretory and prokinetic agents and dietary modifications resulted in no improvement. Her past medical and surgical histories were notable for a previous cholecystectomy and incisional hernia repair.

Physical examination revealed a well-developed but chronically ill-appearing white woman who vomited bilious material numerous times during her interview. She was afebrile with normal vital signs and a weight

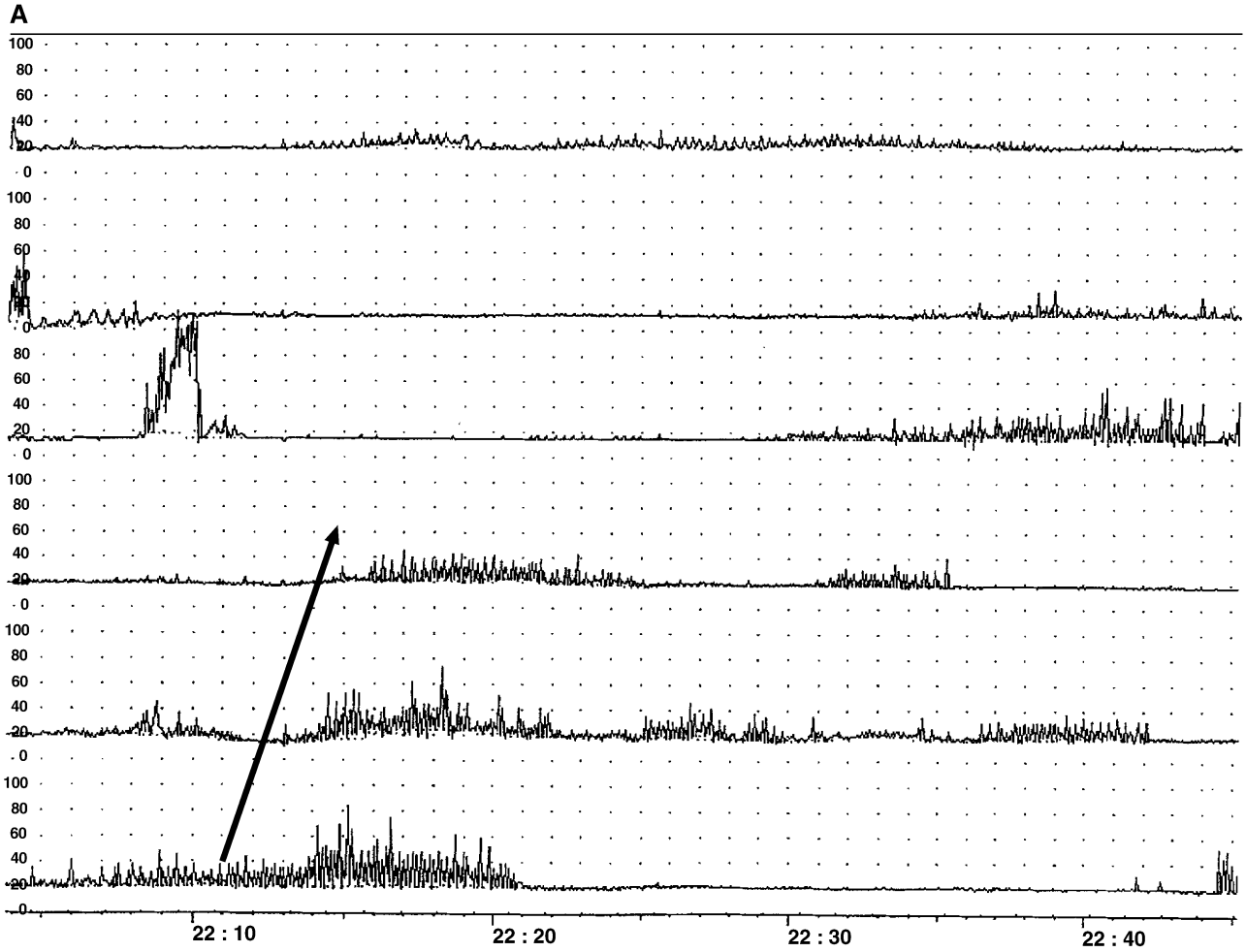

Fig. 1. (**A**) Intestinal manometry tracing from the Roux limb taken from the patient in case 1 demonstrating retrograde propagation of phase III of the migrating motor complex (*arrow*), with premature termination and other disorganized phase III–type activity following. Note that all six sensors are located within the Roux limb and are oriented in a craniocaudal direction (top to bottom). (**B**) For comparison, an intestinal manometry tracing taken from a healthy individual demonstrates normal phase III activity with antegrade propagation.

of 66.8 kg. Her general examination was unremarkable, and her abdominal examination was notable only for healed scars. Her abdomen was soft and nondistended with normoactive bowel sounds.

Numerous laboratory studies were normal. A barium-contrast small bowel series revealed a delay in emptying from the esophagojejunal "pouch" but no anastomotic narrowing, bowel obstruction, or dilated bowel. Upper endoscopy revealed copious bilious secretions in her esophagus. The EJ anastomosis was widely patent. About 20 cm distal from the EJ anastomosis, a side-to-side anastomosis was encountered. One limb appeared to come to a blind end after about 10 cm. The other limb was normal. A solid-state manometric catheter was then placed with endoscopic guidance so that the three distal pressure sensors were positioned within the "normal" limb and the three proximal sensors were positioned within the segment between the EJ anastomosis and the distal anastomosis (i.e., Roux limb). Similar to patient 1, visual analysis of the tracing revealed normal amplitude and frequency of contractile activity in the Roux limb, paucity of phase II activity, and frequent phase III activity, occurring about once per hour, with numerous abnormalities of propagation of the phase III most notable for the consistent occurrence of retrograde propagation in the proximal three sensors but antegrade propagation in the distal three sensors (Fig. 3).

With the information from both the endoscopy and manometry, a decision was made to surgically explore the patient. Upon surgical exploration, it was apparent that the afferent limb from the ligament of Treitz

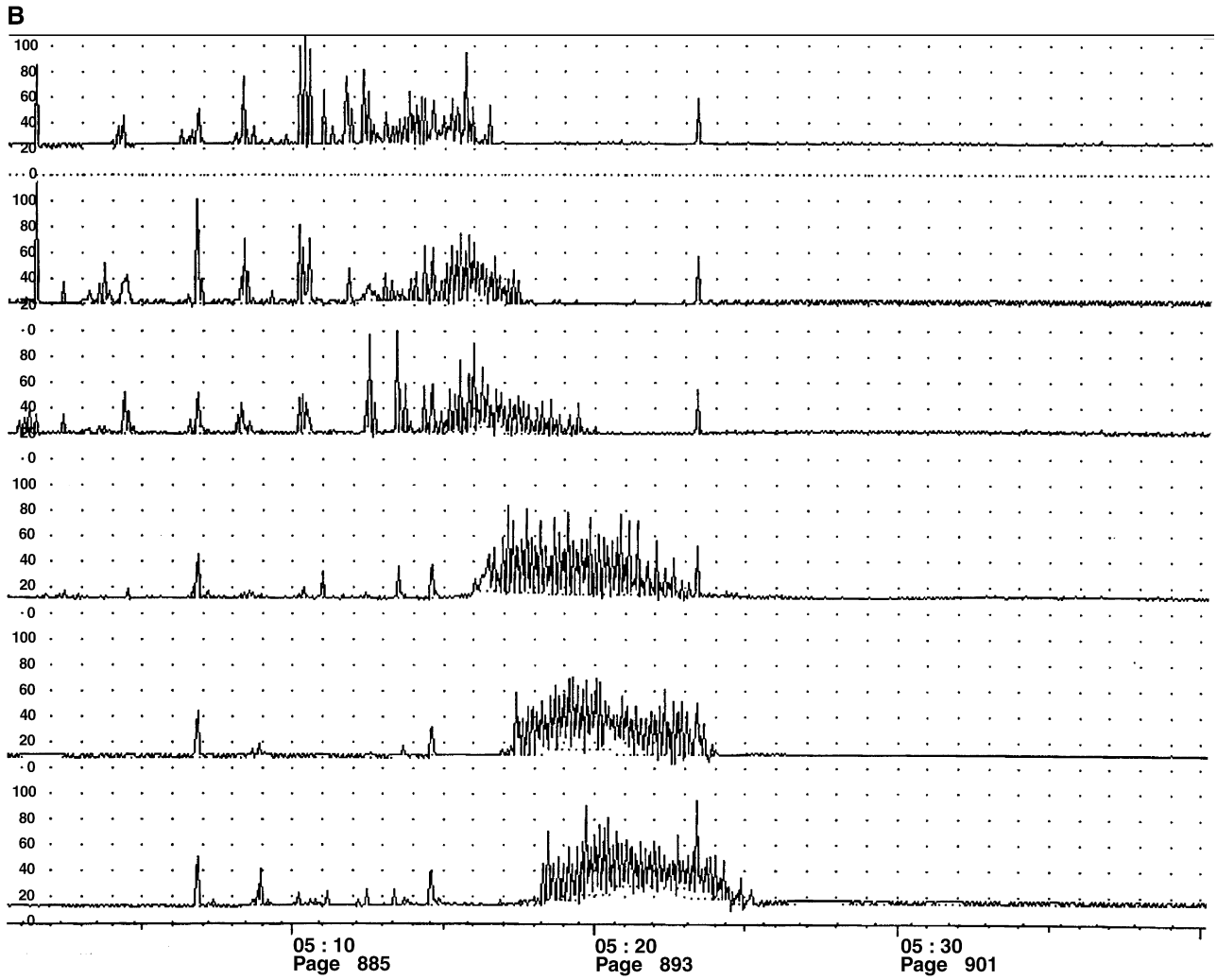

Fig. 1. Continued.

came up to a side-to-side anastomosis and then continued as the limb leading up to the EJ anastomosis, whereas the distal bowel was merely anastomosed distally—a situation identical to Fig. 2, *A* with the distance between points A and B of about 20 cm. Following the correction of the positioning of the Roux and duodenojejunal limbs, the patient recovered uneventfully, the vomiting resolved within 24 hours of the operation, and she was discharged home shortly thereafter. She has been free from vomiting ever since.

DISCUSSION

These case reports illustrate the devastating consequences of a poorly constructed Roux-en-Y esophagojejunostomy and demonstrate the utility of intestinal manometry in aiding the diagnosis of problems related to the Roux limb. To our knowledge, these are the first cases reported in the literature that detail the consequence, diagnosis, and management of inadvertent antiperistaltic Roux-en-Y esophagojejunostomy reconstruction following a total gastrectomy. Interestingly, a review of the literature did reveal two cases of inadvertent antiperistaltic Roux-en-Y choledochojejunostomy manifesting as recurrent cholangitis.[1] Technical aspects of Roux limb construction have been well described. In general, the jejunum should be divided a short distance from the ligament of Treitz. The distal end is then mobilized for anastomosis to the esophagus, stomach, or pancreaticobiliary system, while the proximal end is anastomosed to the Roux limb at a point distal enough to limit the reflux of enteric contents. In our cases, it was thought that the inadvertent Roux reversal at the initial operation occurred because division of the proximal jejunum at the time of creation of the original Roux loop had been carried out too far distal to

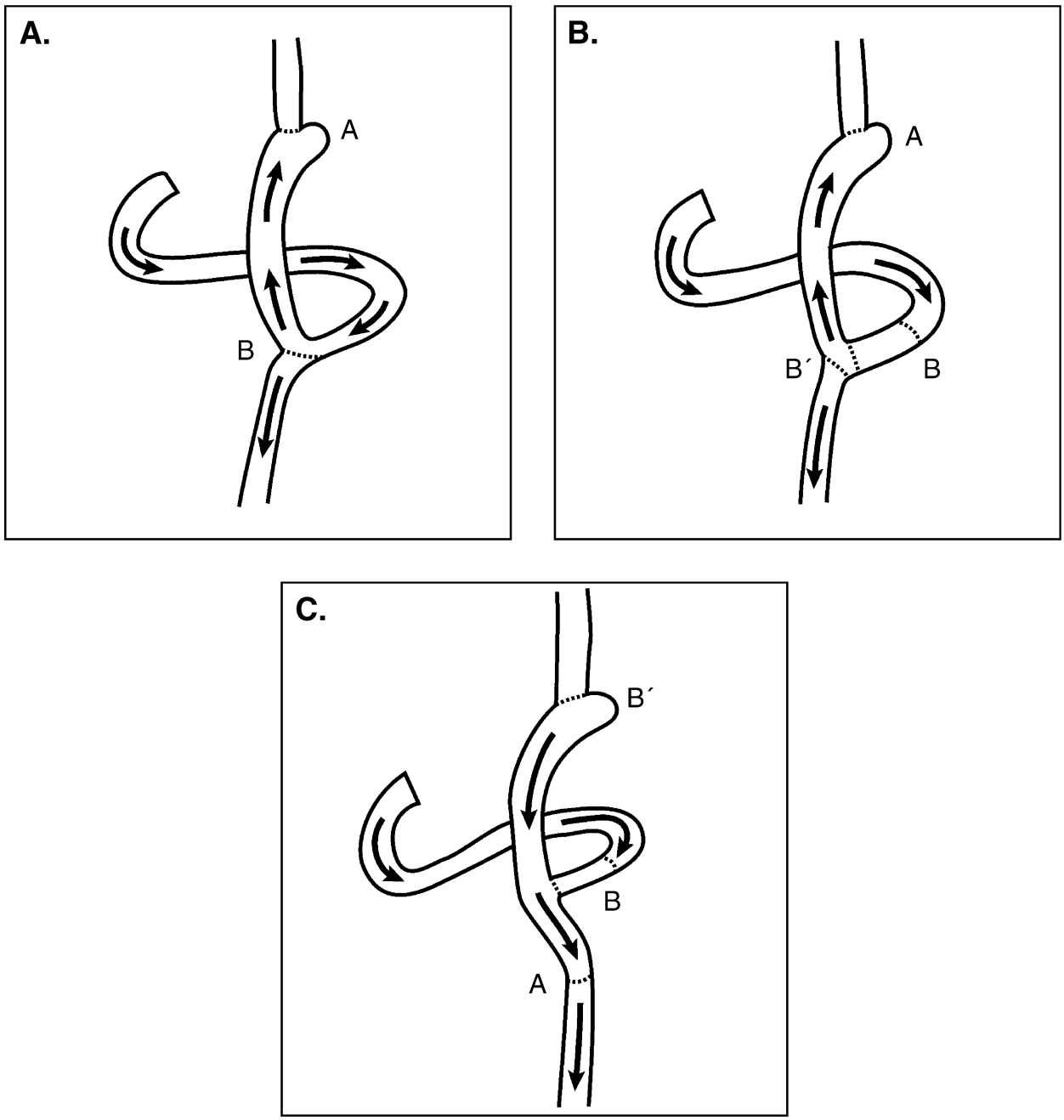

Fig. 2. (**A**) Diagram of the findings at exploratory laparotomy in case 1 showing the Roux limb constructed in an antiperistaltic orientation. The distance from A to B, representing the Roux limb, was 100 cm. Note that in case 2, this length was only about 20 cm. (**B**) Diagram of the findings at the completion of the first exploration consisting of repair of the bilioenteric fistula and shortening of the Roux limb (A to B′ = 60 cm). Note that the antiperistaltic positioning remains. (**C**) Diagram of the findings after the second operation with isoperistaltic repositioning of the Roux-en-Y esophagojejunostomy (B′ to A). The flow of bowel contents is shown (*arrows*).

the ligament of Treitz, allowing the wrong end of the Roux loop to be carried superiorly to the esophagus without an overt twist in the mesentery (Fig. 2, *A*). Case 1 also highlights the difficulty that may arise in the identification of a poorly constructed Roux-en-Y despite thorough examination at the time of repeat exploratory laparotomy. We suspect that the difficulty in identifying the reversed Roux limb in patient

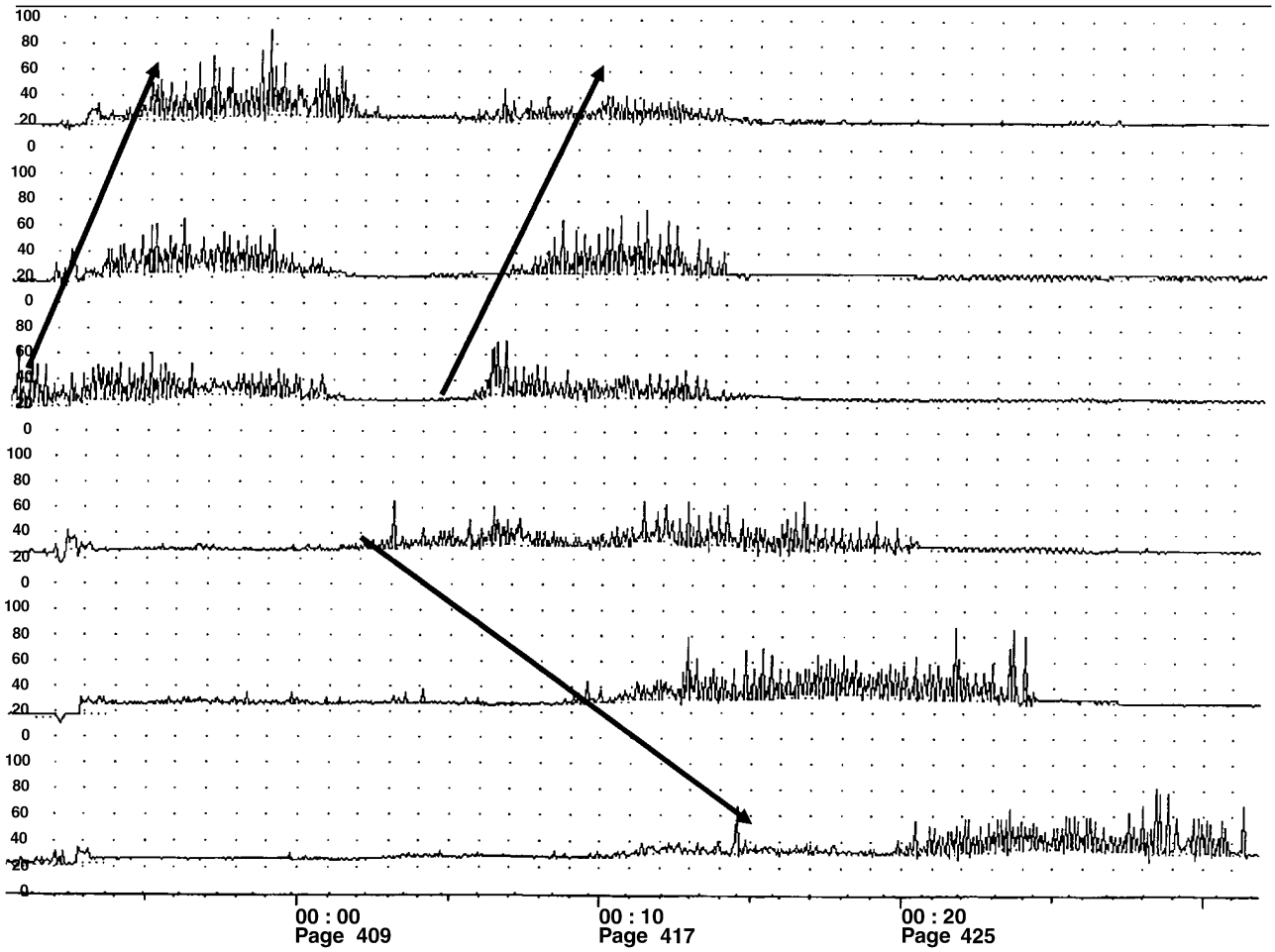

Fig. 3. Intestinal manometry tracing from the Roux limb taken from patient 2 demonstrating retrograde (top three sensors) and antegrade (bottom three sensors) propagation of the phase III of the migrating motor complex. Note that all six sensors are oriented in a craniocaudal direction (top to bottom). The direction of propagation is indicated (*arrows*). See the text for details of the sensor positions relative to the Roux limb.

1 relates to the patient's multiple recent abdominal surgeries. The most strikingly consistent clinical feature in both cases was the presence of persistent, severe, bilious vomiting unrelated to eating and without preceding nausea or abdominal pain that began immediately postoperatively. This clinical scenario should alert the treating physician to the possibility of an inadvertent reversal of the Roux limb.

The Roux-en-Y operation was originally described in 1892 by Swiss surgeon Cesar Roux. It was speculated that a major advantage of this type of reconstruction following partial or total gastrectomy would be the prevention of reflux of pancreaticobiliary contents into the gastric remnant or esophagus. Despite its potential merit, a major problem related to this procedure has been the development of the Roux-en-Y syndrome. First described in 1985, this syndrome is characterized by chronic abdominal pain, fullness, nausea, and vomiting worsened by eating.[2] The incidence of this syndrome varies widely, ranging from 10% to 67%,[3,4] and the risk appears to increase as the length of the Roux limb increases.[5] While the Roux-en-Y syndrome ultimately proved not to be the underlying problem in our patients, it was a diagnostic consideration when they first presented.

A number of studies have evaluated transit and motility patterns in the Roux limb of patients following gastric resection, albeit, mainly in distal gastrectomy patients rather than total gastrectomy patients, as in our case. Available evidence is conflicting and derived from studies using small numbers of patients. Although motor abnormalities are present in most symptomatic and asymptomatic patients following Roux-en-Y gastrojejunostomy, the basic motor patterns (i.e., interdigestive migrating motor complex [MMC] and fed response) appear to be preserved in

most patients. While differences in study methods limit direct comparisons, in general, abnormalities of the frequency[2,6,7] and propagation[2,6–8] of phase III of the MMC and postprandial response, including shorter duration of the fed response and an overall decrease in postprandial motility,[6,9–11] have been consistently demonstrated. Whether these differences relate to the degree of gastric resection (i.e, distal or total), underlying diagnosis, or some other factor remains unclear.[11,12] The recent demonstration of slower propagation/migration velocity of phase III has been suggested as a useful discriminator between symptomatic and asymptomatic patients.[6] Symptomatic patients also seem to have more incomplete propagation of the phase III compared with asymptomatic patients.6 Only a single study has assessed motility before Roux-en-Y creation, finding that it was normal, thus suggesting that the postoperative Roux limb dysmotility was not a preexisting condition.[6] More severe motility disturbances have been noted in those patients with multiple surgeries before the Roux-en-Y reconstruction, suggesting that the other surgeries may somehow have played a role in the Roux limb dysmotility.[8]

Although the clinical utility of gastroduodenal and intestinal manometry remains somewhat controversial,[13–16] in our cases, intestinal manometry provided key information that led to reexploration, to determine whether the Roux limb was anastomosed in an antiperistaltic orientation. In our patients, similar to reports of patients with the Roux-en-Y syndrome, manometry of the Roux limb demonstrated significant abnormalities of phase III of the MMC consisting of increased frequency and abnormal propagation. Importantly, and unlike previous reports of motility in the Roux-en-Y syndrome, retrograde propagation of phase III was the most notable finding in our patients. Although retrograde propagation of phase III has been infrequently described in the Roux limb,[9] because of the predominance of the retrograde propagation, Roux-en-Y syndrome was thought to be an unlikely explanation. Although manometry cannot be credited with diagnosing the errant Roux limb construction, it certainly aided our decision to proceed with surgical exploration and reexamination of the orientation of the Roux limb.

In summary, we have presented two cases that illustrate the devastating consequences of a poorly constructed Roux-en-Y esophagojejunostomy and demonstrate the utility of intestinal manometry in aiding the diagnosis of problems related to the Roux limb. The clinical scenario of persistent, severe, bilious vomiting unrelated to eating and without preceding nausea or abdominal pain that begins immediately postoperatively should alert the treating physician to the possibility of an inadvertent reversal of the Roux limb.

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Laparoscopic Spleen-Preserving Distal Pancreatectomy

Amit Khanna, M.D., M.P.H., Leonidas G. Koniaris, M.D., F.A.C.S., Attila Nakeeb, M.D., F.A.C.S., Luke O. Schoeniger, M.D., Ph.D., F.A.C.S.

Distal pancreatectomy with spleen preservation may be the preferred procedure for certain benign tumors and cystic lesions of the pancreatic body or tail. Alternatively, laparoscopic removal including either distal pancreatectomy with splenectomy or splenic-preservation with ligation of the splenic vessels have also been described. We describe, herein, our method to perform spleen-preserving laparoscopic distal pancreatectomy that preserves the splenic vessels and hence splenic function. The described technique of spleen-preserving distal pancreatectomy has been used in two patients with favorable results. Both patients underwent laparoscopic distal pancreatectomy with splenic conservation for an oligocystic serous cystadenoma and serous cystadenoma. Operative time was 3–6 hours with total blood loss of less than 200 cc in both cases. The length of stay in the hospital was 4–8 days and both patients returned to work within 3 weeks. Laparoscopic spleen-preserving distal pancreatectomy should be considered for younger patients with select body or tail lesions that are not candidates for less extensive procedures. (J GASTROINTEST SURG 2005;9:733–738)

KEY WORDS: Cancer, cystic pancreatic neoplasms, laparoscopy, pancreas

Laparoscopic distal pancreatectomy may be the preferred technique regarding the treatment of small benign tumors and cystic neoplasms in the body or tail of the pancreas in select patients[1,2] and, as such, is commonly performed. Most often this is achieved with splenectomy, dissecting from lateral to medial. In younger patients, splenic preservation may be beneficial.[3] To date, however, most reports of laparoscopic splenic-preserving distal pancreatectomy have involved either the en-bloc resection of the splenic artery and vein and relied upon the short gastric vessels for post-pancreatectomy splenic blood flow[4] or commenced pancreatic dissection at the splenic hilum. Preservation of the short gastrics alone, although technically spleen preserving, does not preserve essential splenic immunologic function. An intact splenic artery and portal vein have been demonstrated to be critical for splenic clearance of encapsulated organisms.[5] We have begun to apply a laparoscopic approach to spleen-preserving distal pancreatectomy in select patients with pancreatic lesions. The technique involves the medial-to-lateral separation of the pancreas from the splenic vessels with their preservation. Our technique is presented herein.

MATERIAL AND METHODS

Port placement is diagrammed in Fig. 1 (inset). A 5 mm 30° laparascope is used. The superio-lateral port is 12 mm in diameter. All other ports are 5 mm. As with all pancreatic surgeries, the procedure is initiated with a careful inspection of the peritoneal surfaces, omentum, mesentery, and the viscera to rule out metastatic disease. Intraoperative ultrasound can be used to evaluate the liver and localize the lesion in the pancreas.

From the DeWitt Daughtry Department of Surgery, University of Miami, Miami, Florida (L.G.K.); Department of Surgery, University of Rochester, Rochester, New York (A.K., L.O.S.); and Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana (A.N.). Reprint requests: Luke O. Schoeniger, M.D., Box SURG, 601 Elmwood Ave, Rochester, NY. e-mail: Luke_Schoeniger@urmc.rochester.edu

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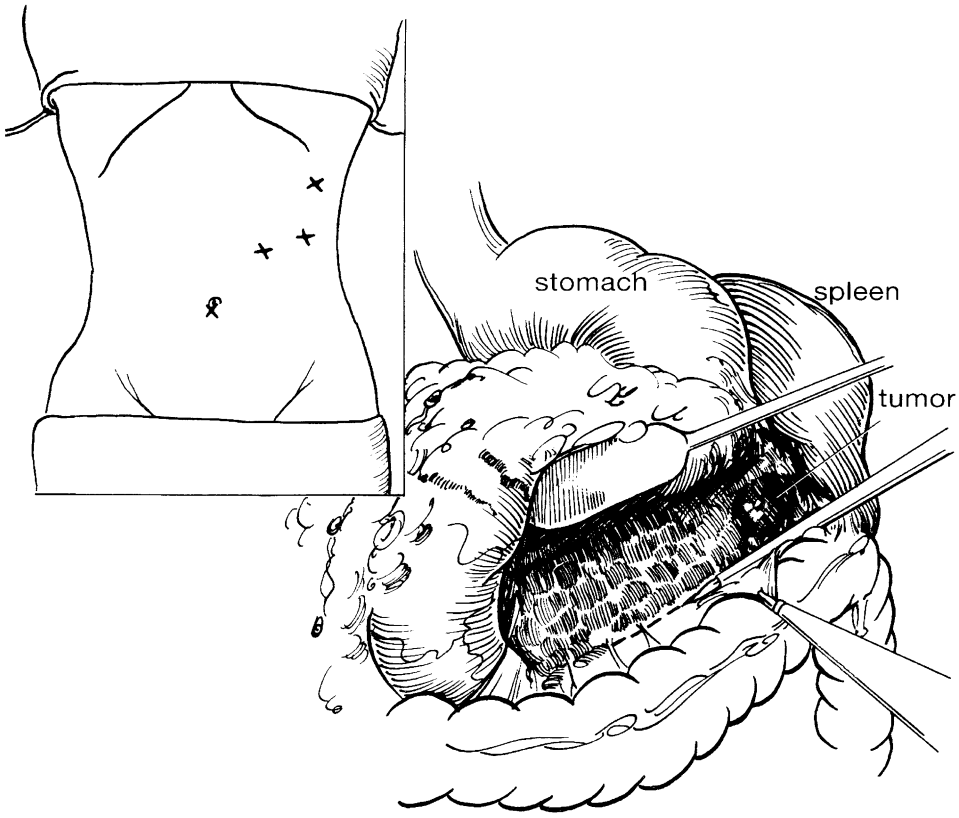

Fig. 1. (Inset) Trochar placement for spleen-preserving laparoscopic distal pancreatectomy. Depiction of laparoscopic exposure for distal pancreatectomy after division of the gastrocolic omentum. A paddle retractor placed in the lesser sac elevates the stomach. The splenic flexure and transverse colon (splenocolic ligament) have been mobilized and the colon reflected inferiorly to improve exposure of the lesser sac. Retroperitoneal dissection at the inferior edge of the pancreas has been initiated.

The body and tail of the pancreas are exposed by opening the lesser sac. Staying outside of the gastroepiploic vessels, the gastrocolic omentum is divided and widely mobilized with the harmonic scalpel. The inferior most short gastric vessels may require division so that the stomach can be retracted and the body and tail of the pancreas can be completely visualized. A paddle retractor is placed through the left superior-lateral 12 mm port into the lesser sac and used to elevate the stomach anterior-medially. Next, the splenocolic ligament is divided and the colon is reflected inferiorly. After these maneuvers, the inferior pancreatic margin should be exposed. A retroperitoneal dissection is then initiated after the incision of the peritoneum along the inferior pancreatic border (Fig. 1).

Sharp and blunt dissection along the inferior pancreatic border is used to separate the pancreatic body from the retroperitoneum. Laparoscopic ultrasound and direct visual inspection combined with preoperative imaging may be used to determine the extent of the resection. Initial dissection should be directed so as to be medial to the pancreatic lesion. Once this location is determined, blunt and sharp dissection is used to elevate the pancreatic body. With this blunt dissection the splenic vein will be easily encountered and visualized (Fig. 2). Care must be exercised to prevent its inadvertent injury. After identification of the splenic vein, careful dissection with the use of a right angle clamp is performed to circumferentially dissect around the splenic vein. Such dissection will, in addition, help identify the splenic artery, which is also circumferentially dissected and may be controlled with a vessel loop. These precautionary measures should allow for quick control of bleeding should a subsequent vascular tear occur. Using laparoscopic Metzenbaum scissors for sharp dissection and the harmonic scalpel to divide vessels, the pancreatic branches of the splenic vein are sequentially identified and dissected free (Fig. 3). A medial-to-lateral approach is used with dissection moving toward the splenic hilum. During this dissection, branches of the splenic artery, which run just superior to the vein, are treated in a similar fashion. It is important to note

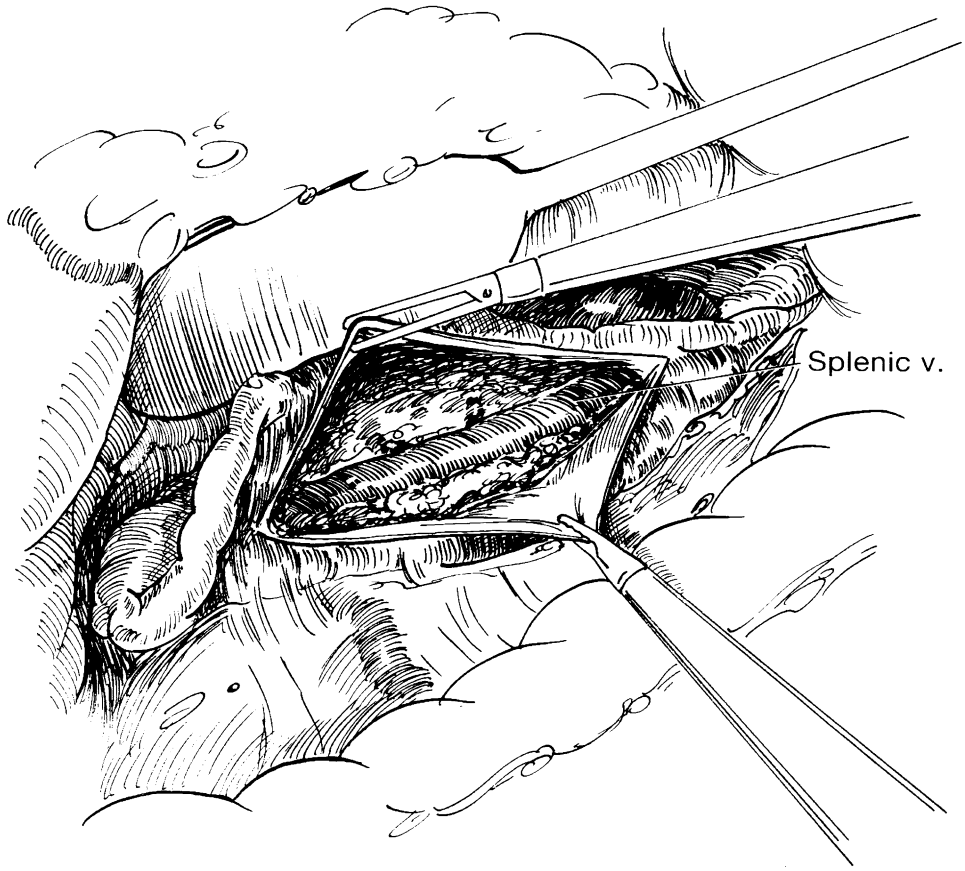

Fig. 2. Identification of the splenic vein after mobilization of the pancreatic body from the retroperitoneum.

that we have not deemed it necessary to place metal clips on any of these vessels, achieving excellent hemostasis with the harmonic scalpel without the risk of clip dislodgement or interference with subsequent firing of the linear stapler.

Once adequate mobilization of the pancreatic body from the splenic vessels has occurred, the paddle retractor is temporarily exchanged for a vascular endoscopic stapler that is placed across the body of the pancreas sparing the main splenic vessels (Fig. 4). Alternatively, the harmonic scalpel can also be used to divide the pancreatic parenchyma. Once the proximal pancreatic tissue is divided, the specimen is grasped and gently retracted anteriorly to further allow dissection of the vessels in their course to the spleen. When working near the hilum to identify and divide these attachments using the harmonic scalpel (Fig. 5), special care must be taken. In contrast with other techniques, having the pancreas already transected facilitates retraction and vision during hilar dissection. After completion of the spleen-preserving distal pancreatectomy, the specimen is placed and removed in a standard endo-catch device. The pancreatic remnant can then be oversewn with a series of interrupted horizontal mattress sutures using an absorbable suture (Vicryl). A single round Jackson Pratt drain is placed at the stapled pancreas and brought out through one of the 5 mm lateral ports. Use of a size 12 mm port results in a greater cosmetic result and minimal postoperative pain.

RESULTS

The described technique has been used in the management of symptomatic pancreatic lesions in 2 patients. The first patient was a 21-year-old otherwise healthy female who presented with a complaint of epigastric tenderness. Right upper quadrant ultrasound detected a cystic pancreatic lesion of the pancreatic body. A computed tomography (CT) scan was performed which demonstrated a complex cystic lesion of the pancreatic body that seemed to connect with the pancreatic duct. The patient was offered aspiration of the mass but expressed a desire to undergo definitive resection rather than additional diagnostic procedures and therefore underwent a laparoscopic spleen-preserving distal pancreatectomy. The procedure took 3 hours and there was a

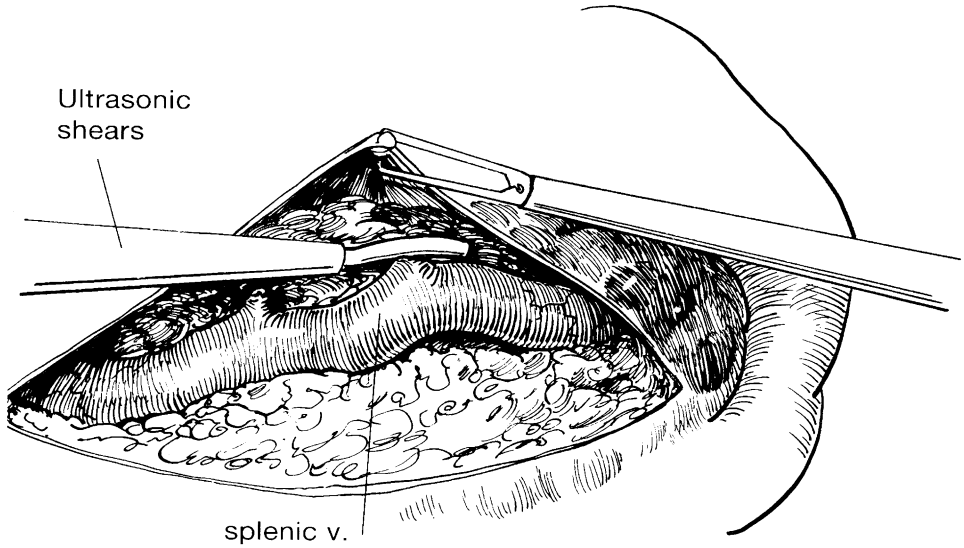

Fig. 3. Branches of the splenic vein and artery undergoing ligation using the harmonic scalpel.

blood loss of 50 ml. On postoperative day 3 the patient's diet was advanced. The patient was discharged on postoperative day 4 and returned to work on postoperative day 14.

The second patient was a 43-year-old female with a history of recurrent sigmoid diverticulitis. A preoperative CT scan of the abdomen was performed that demonstrated a complex cystic lesion of the pancreatic body and tail. The patient underwent a laparoscopic sigmoid colectomy and spleen-preserving distal pancreatectomy. The procedure took 6 hours and there was a blood loss of 200 cc. The patient was discharged on postoperative day 8 and returned to work by the third postoperative week.

In the first patient, pathology revealed an oligocystic serous cystadenoma that is an unusual variant whose resection is clearly required because of its gross and radiographic similarity to the potentially premalignant mucinous cystadenoma. In the second patient, pathology revealed a serous cystadenoma.

DISCUSSION

Patients presenting with pancreatic adenocarcinoma or mucinous cyst-adenocarcinoma of the body or tail that seems resectable using a CT scan may benefit from laparoscopic staging procedures.[6] In such patients, however, an open distal pancreatectomy and splenectomy most likely remain the preferred surgical approach.[1] Laparoscopic spleen-preserving distal pancreatectomy, in contrast, is only one of many techniques that may be employed to treat less aggressive tumors such as smaller islet cell tumors or premalignant cystic lesions of the pancreatic body or tail. Less invasive options may include aspiration and biopsy, observation of the cysts, particularly serous collections, or enucleation of small cysts or islet lesions.[7] Limitations regarding these other less invasive approaches, however, include the development of a pancreatic duct leak and an insufficient margin of resection, possibly resulting in local recurrence and the uncertainty of diagnosis.

We have used a laparoscopic spleen-preserving distal pancreatectomy for younger patients with body or tail lesions that are not candidates for a less extensive procedure (i.e., enucleation), generally because of the proximity of the pancreatic duct to the lesion or because of the uncertainty of diagnosis. It is worth noting that the presence of considerable pancreatitis has been a relative contraindication for a spleen-preserving distal pancreatectomy, especially laparoscopically, because of the increased difficulty encountered with regard to separating the splenic blood vessels from the pancreas. In older patients, no clear long-term benefit seems to be associated with splenic preservation although a trend toward lower perioperative morbidity has been reported.[3] This described approach has been successfully attempted in 2 patients. Both patients exhibited low-risk lesions and were young which, with regard to enucleation, would possibly have resulted in a ductal disruption. Both patients achieved a rapid postoperative recovery with a 4-day hospital stay and were able to return to work within several weeks of the procedure. Our search of the literature has yielded a single report of medial-to-lateral dissection as part of a technique that differs from that presented herein.[8]

Important technical details of our approach include the medial-to-lateral pancreatic dissection. The

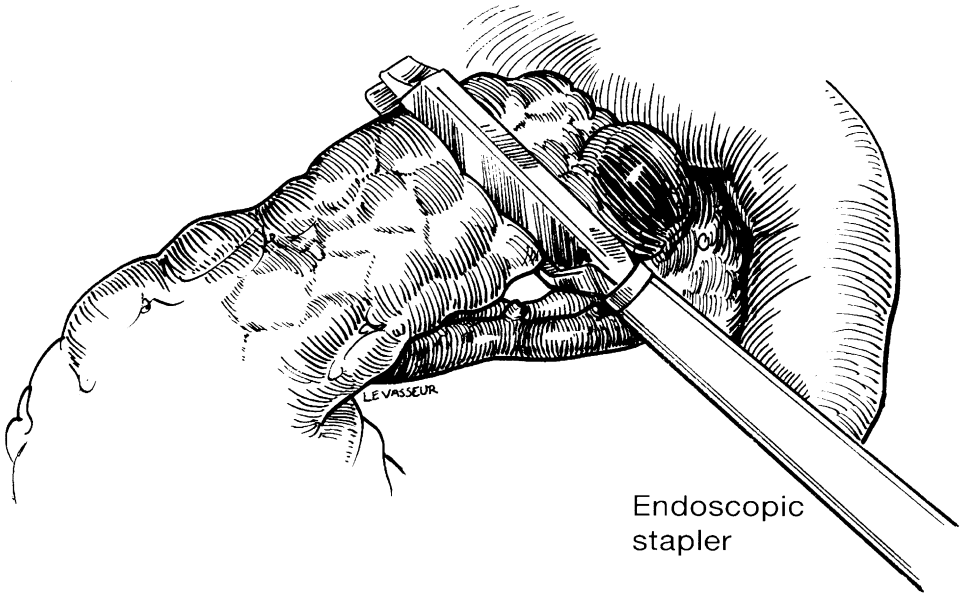

Fig. 4. After identification of the resection margin, a vascular endoscopic stapler is applied across the body of the pancreas sparing the main splenic vessels. Alternatively, the harmonic scalpel may be applied to divide the pancreas and afterwards by the application of interrupted mattress sutures.

pancreas and splenic vessels are identified medial to the lesion early in the dissection. It is noteworthy to state that we have identified the splenic vessels early in the procedure to assure hemostatic control in the event that the subsequent dissection results in inadvertent bleeding. This is in contrast to other technical approaches.[9] A major observation is that sutures or clips are not required for ligation in these

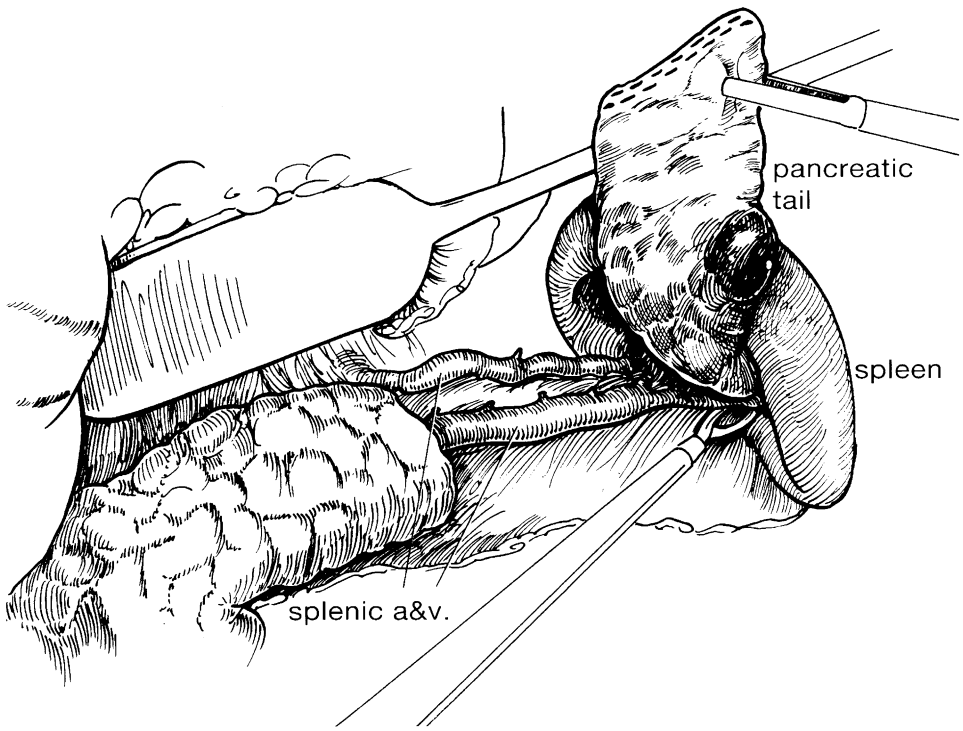

Fig. 5. After proximal pancreatic division, the specimen is retracted anteriorly to further allow dissection of the vessels in their course to the splenic hilum.

occurrences and we have, instead, successfully relied on the harmonic scalpel. Major issues regarding the application of this approach include careful patient selection and optimal visualization with the use of the laparoscopic retractor and ultrasound.[10] Spleen-preserving distal pancreatectomy may be considered for the subset of younger patients with select body and tail lesions.

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Review Article

Gallstones in Chronic Liver Disease

Michael Anthony Silva, M.B.B.S., M.S., F.R.C.S.Ed, Terence Wong, M.B.B.S., Ph.D., M.R.C.P.

Gallstones occur more commonly in patients with cirrhosis. The incidence increases with severity of liver disease, and the majority remain asymptomatic. When symptoms do occur, morbidity and mortality are much higher than in noncirrhotic patients. Asymptomatic gallstones in cirrhotic patients are best managed conservatively with close follow-up and surgery if symptoms occur. The management of asymptomatic gallstones found incidentally at abdominal surgery for another indication is controversial. Laparoscopic cholecystectomy is the treatment of choice for symptomatic cholelithiasis in patients with well-compensated liver disease, whereas patients with choledocholithiasis are best managed endoscopically. Symptomatic cholelithiasis in the decompensated patient remains a challenge, and these patients are best managed in specialized hepatobiliary centers. This review examines the evidence currently available on gallstones in chronic liver disease and the factors that influence its management. (J GASTROINTEST SURG 2005;9:739–746)

KEY WORDS: Cholelithiasis, choledocholithiasis, cirrhosis, cholecystectomy, cholecystostomy

Gallstones (GS) are common in the general population, and it is estimated that about 10–20% of the adult population in developed countries have GS.[1–3] The prevalence is higher in women, the obese, and older patients.[1–3] The reported frequencies of GS in chronic liver disease (CLD), in comparison, tends to be higher.[1–6] In autopsy studies, the frequency of GS in patients with CLD ranges from 3.6% to 46%, with a 1.2- to 3-fold increase compared with the general population.[1–3,7] Studies using ultrasonography report a prevalence GS ranging between 22% and 54%.[1,2,4–6,8–11] Despite this high prevalence, the management of GS in patients with CLD remains controversial,[1–4] and the aim of this review was to examine the evidence for current treatment strategies.

THE EPIDEMIOLOGY OF GALLSTONES IN PATIENTS WITH CHRONIC LIVER DISEASE

GS are found in 10–20% of the general adult population.[1–3,12] In comparison, autopsy studies have shown up to a threefold increase in GS among cirrhotic patients compared with noncirrhotic controls.[7,10,13,14] Similarly, ultrasonographic studies have also confirmed the higher prevalence of GS in patients with CLD[5,6,8–10,15,16] (Table 1).

These studies report the prevalence of asymptomatic GS. The prevalence of clinically manifest GS in patients with CLD is largely unknown.[17] A recent retrospective review of medical records of 38,459 inpatients with various forms of liver disease found the prevalence of symptomatic GS to be 7.5%,[18] although the possibility of occasional detection bias cannot be excluded. In a longitudinal cohort study of a group of 34 patients with asymptomatic GS and CLD, 18% developed symptoms over 6 years.[19] Although the number of patients in the study was small and the duration of follow-up was short, this figure is comparable to that of asymptomatic GS in noncirrhotic patients.[1] In noncirrhotic patients, there is a mean delay of about 8 years between stone formation and the onset of symptoms.[20] It is not clear whether this holds true for GS in CLD.

There exists a 3:1 female predominance for the incidence of GS in the population without CLD.[1,2,12] This pattern is similar in patients with CLD,[11,21–23] although some early reports indicated that the incidence of GS was higher in males.[5] GS occur more frequently in patients with cirrhosis than in patients

From The Liver Unit, Queen Elizabeth Hospital, University Hospital Birmingham NHS Trust, Edgbaston, Birmingham, United Kingdom. Reprint requests: Michael A. Silva, M.S., F.R.C.S.Ed., c/o Liver Surgical Secretaries, 3rd Floor, Nuffield House, Queen Elizabeth Hospital, University Hospital Birmingham NHS Trust, Edgbaston, Birmingham B15 2TH, United Kingdom. e-mail: M.A.Silva@bham.ac.uk

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Table 1. Prevalence of gallstones in chronic liver disease (CLD)

Author (first)	Year	Type of study	No. of subjects	Prevalence of gallstones (%)
Bouchier IAD[7]	1969	Autopsy	Patients with CLD (n = 235)	29.4
			Controls (n = 4460)	12.8
Iber FL[10]	1977	Autopsy	Patients with CLD (n = 460)	33
			Controls (n = 316)	13
Iber FL[10]	1990	Autopsy	Patients with CLD (n = 299)	46
			Controls (n = 178)	21
Fornari F[5]	1990	Ultrasound	Patients with CLD (n = 410)	31.9
			Controls (n = 414)	20

with chronic hepatitis,[9] and pigment stones occur more frequently in GS of patients with CLD, while its incidence also increases with age.[8,15,24,25]

GALLSTONES IN RELATION TO ETIOLOGY AND SEVERITY OF LIVER DISEASE

The risk of GS appears to be independent of the underlying etiology of liver disease.[4,15,26] In a study looking at the etiology of CLD, in 313 cirrhotic patients, its cause did not seem to be important as a risk factor for GS formation.[26] In another study of the prevalence of GS in CLD in relation to the etiology of disease, 356 cirrhotic patients were compared with 247 cases of chronic hepatitis B and C without cirrhosis; a multivariate analysis showed that the duration and severity of cirrhosis were the only factors independently related to the development of GS in CLD, whereas hepatitis B surface antigen (HBsAg) positivity behaved as a negative factor.[9] Several other studies have confirmed that the risk of developing GS is correlated with severity of CLD as graded by the Childs-Pugh classification, rather than the etiology of the disease.[5,6,8,9,18,21]

The etiology of symptoms in patients with GS is unknown.[27] It may be partly due to chance, depending on the movement of stones and their impaction in Hartmann's pouch or in the cystic duct.[1] It follows that the relative size of the calculi and the caliber of various parts of the biliary tree may be important.[1] It is, however, clear that other factors play a role. Stasis may precipitate symptoms and is considered particularly relevant in the etiology of postoperative cholecystitis.[28–30] Stasis to bile flow is increased in CLD and may be a cause for the increased incidence of GS in these patients.[31–35] Advanced age, female gender, viral etiology of cirrhosis, family history of GS, and duration of GS disease are, however, factors that are associated with symptomatic gallbladder disease.[17] Male gender and alcoholic cirrhosis have interestingly been found to have an inverse relationship to the presence of symptoms.[17]

MECHANISMS OF GALLSTONE FORMATION IN CHRONIC LIVER DISEASE

The mechanisms leading to the increased incidence of GS in CLD are not well understood.[18] About 80% of GS in patients with CLD are pigment stones compared with 20% in noncirrhotic patients.[17,18,21,25,36] Patients with liver cirrhosis may also have increased hemolysis secondary to hypersplenism, resulting in a higher incidence of pigment stones.[4,10] Studies have shown that however efficient, the liver does not convert all the unconjugated bilirubin into bilirubin monoglucuronides and diglucuronides: a small fraction of the unconjugated moiety escapes conjugation and 'spills' into bile.[37] In CLD, the fraction of bilirubin escaping conjugation increases. The resultant excess unconjugated bilirubin in bile is vulnerable to polymerization and/or to co-precipitation with free ionized calcium.[37,38] Deconjugation may also be catalyzed by glucuronidases of bacterial or mucosal origin,[39] and bilirubin monoglucuronide may also undergo nonenzymatic hydrolysis to form unconjugated bilirubin. Even in normal bile, therefore, the low concentration of unconjugated bilirubin still exceeds its aqueous solubility by 100- to 1000-fold.[39,40] This unconjugated bilirubin has been identified as a component of biliary sludge, which is believed to precede GS, especially pigment stones.[39] Additionally, decreased apolipoprotein A-I and A-II levels in advanced CLD have also been implicated as cause for a higher incidence of GS in these patients.[22]

Pigment GS could be either black or brown. Black pigment stones, which commonly occur in the gallbladder only, are small (approximately 3 mm) and occur with increased frequency in patients with CLD

and in those with hemolytic disease.[9,11,15] Brown pigment stones are found more often in the biliary tree than in the gallbladder. Brown stones are conventionally associated with bacterial infection and parasitic infestations like fascioliasis (caused by the liver fluke). Recent studies have, however, shown that neither the color nor the chemical composition accurately predicts the presence or absence of gallbladder bacteria and diseases that cause brown pigment stones, like fascioliasis, which may result in CLD, in turn possibly resulting in the formation of black pigment stones.[41,42]

Studies have shown that moderate intake of alcohol actually decreases the risk of GS formation.[22,25,43,44] Alcohol lowers bile cholesterol saturation with a resultant reduction of cholesterol stones[18] and may cause an increase in conversion of cholesterol to bile acids.[45–47] An increased high-density lipoprotein cholesterol serum concentration is associated with moderate alcohol consumption, and this could result in the lower incidence in cholesterol stone formation.[48–50] In contrast to this protective role alcohol may have on GS formation, heavy ethanol intake is a major risk factor for the development of liver disease by promoting fibrosis and cirrhosis, both of which are risk factors for developing GS, especially of the pigmented type.[18,22]

It has been suggested that high levels of estrogens and progesterone in CLD could play a role in the higher incidence of GS in these patients, by the impairment of gallbladder emptying similar to that observed in pregnancy.[5] A study evaluating the fasting volume and meal-stimulated emptying of the gallbladder, plasma levels of estradiol, progesterone, and basal and postprandial secretion of cholecystokinin in Child-Pugh class A cirrhotic patients compared them with results for normal subjects.[34] Normal kinetics of postprandial emptying was demonstrated in both groups, although cirrhotic patients showed an increased fasting gallbladder volume and higher levels of basal and postprandial cholecystokinin.[34] The circulating estradiol and progesterone levels were not significantly elevated to be implicated as causative of GS in CLD.[34]

The study of gallbladder kinetics in the presence of CLD and cirrhosis has shown on ultrasonography and radionuclide cholescintigraphy that its emptying is sluggish.[51–53] On ultrasonography, the unstimulated gallbladder in patients with CLD and cirrhosis has also been found to have significantly increased volumes with signs of a hypotonia.[52,54] There is some evidence to suggest that gallbladder contraction is also under neural control.[32] It has also been demonstrated that patients with moderate to severe liver dysfunction have impaired autonomic function.[31] Autonomic neuropathy may therefore contribute to the formation of GS in patients with advanced cirrhosis, perhaps by impairing gallbladder and sphincter of Oddi motility.[32] Gallbladder disease has also been found to be increased in patients with CLD and coexistent autonomic neuropathy.[32]

CLINICAL DIAGNOSIS OF GALLSTONES IN PATIENTS WITH CHRONIC LIVER DISEASE

A recent study has described upper abdominal pain that is especially postprandial as more common in those with CLD than in normal controls.[55] Early symptoms due to GS disease need to be differentiated from those of dyspepsia, peptic ulcer disease, or irritable bowel syndrome.[56] In CLD patients, upper abdominal pain in the absence of the above causes may result from gastric motility dysfunction.[55] An alternative explanation for these postprandial symptoms include increased portal blood flow and volume changes. Duplex ultrasound and magnetic resonance imaging have shown that patients with chronic hepatitis C have a greater volume change to the left lobe of the liver compared with normal controls. This in theory may result in more congestion and stretch of the Glission's capsule, resulting in the symptoms of pain.[57] With these in mind, the clinical presentation, liver function tests, and imaging techniques are usually sufficient to diagnose symptomatic GS disease in patients with CLD.

THE NATURAL HISTORY OF GALLSTONES IN CIRRHOTIC PATIENTS

The management of GS in patients with CLD is a frequent dilemma. The risks of an operation need to be weighed against the likelihood of GS progressing to acute cholecystitis or bile duct obstruction. There is, however, a paucity of data on the natural history of GS in this cohort of patients. Jaundice in this subpopulation of patients is more commonly due to hepatocellular dysfunction than to bile duct obstruction.[35,58] Ultrasonography and magnetic resonance cholangiopancreatography are the preferred methods for the diagnosis of choledocholithiasis in patients with CLD rather than endoscopic retrograde cholangiopancreatography.[21] Although the risks of the development of symptoms and complications are low, the mortality associated with acute complications is in comparison higher with symptomatic GS than in

the general population.[17,59] These patients are therefore best managed in units equipped with suitable diagnostic and therapeutic facilities such as that available in specialized hepatobiliary centers.

TREATMENT OF GALLSTONES IN CHRONIC LIVER DISEASE

An overall mortality rate for patients with CLD undergoing anesthesia and operation has been reported to be as high as 11.6%.[60] In a recent meta-analysis of patients with CLD undergoing laparoscopic cholecystectomy, an overall morbidity rate of 21% is described in cirrhotic patients compared with an 8% morbidity in noncirrhotic patients.[61] These morbidities included liver bleeding, bile leaks, wound infection, new onset of ascites, peritonitis, pulmonary embolism, and cardiopulmonary complications.[61] Conversion rates from the laparoscopic procedure to open cholecystectomy was 7% versus 3.6%[61,62] ($P = 0.023$). Mortality rates between the two groups, however, were not different statistically.[61] The patients with CLD compared in this study were principally of Child-Pugh class A and B. The laparoscopic procedure in patients with Child-Pugh class C was avoided, with the potential risks of morbidity and mortality in this group being unacceptable.[62–64] Only one study included six patients of Child-Pugh class C, with one death (17%),[61] but no conclusions can be drawn regarding the outcome of laparoscopic cholecystectomy in this subset of high-risk patients due to the lack of data.

When compared with open cholecystectomy in patients with CLD, the laparoscopic procedure is associated with less operative blood loss, a shorter operative time, and a decreased length of hospital stay.[59,61] There was no statistically significant difference in morbidity or wound infection rates between the two groups.[61] There have, however, been no prospective studies comparing laparoscopic and open cholecystectomy in patients with CLD. The data available at present are inadequate for definite conclusions to be made on outcomes comparing these two methods of treatment.

The purpose of cholecystectomy for symptomatic GS is twofold: namely, the relief of symptoms and the prevention of potentially life-threatening complications.[1] Cholecystectomy for asymptomatic GS, however, must be weighed against the hazards of treatment. In noncirrhotic patients, elective cholecystectomy is not indicated because most remain asymptomatic and because mortality rates are low after prompt treatment of those who develop symptoms.[1] Similarly, there is no place for prophylactic cholecystectomy for GS in CLD patients.[1,19]

Many GS are discovered for the first time at laparotomy for an unrelated condition.[1,19] There have been reports describing the subsequent incidence of biliary symptoms in these patients, if left untreated.[1,65] In patients without CLD, due to the reported incidence of biliary symptoms after operation (20–45%), incidental cholecystectomy has been advocated.[1,65–69] In a study involving 34 patients with CLD and GS, 82% remained asymptomatic over a period of 6 years following an abdominal operation for portal hypertension.[19] The role of incidental cholecystectomy in patients with CLD is unclear.[19] The emphasis therefore, in patients with CLD, is for close follow-up with early interventional treatment for GS when symptoms supervene.

The morbidity and mortality rates associated with laparoscopic cholecystectomy in Child-Pugh class A and B patients with symptomatic GS have been shown to be acceptable.[62,63,70–73] The presence, however, of a prolonged prothrombin time, thrombocytopenia, and portal hypertension in CLD patients is a risk factor for increased bleeding in these patients. Therefore, appropriate preoperative preparations and meticulous operative techniques are required to reduce blood loss during the procedure. Laparoscopic cholecystectomy is particularly useful in liver transplant candidates who develop significant biliary symptoms because of its associated fewer postoperative adhesions and rapid recuperation.[61,62] Some groups have even described stenting of the cystic duct endoscopically using biliary stents from gallbladder to duodenum, in this group of patients awaiting liver transplantation, to relieve symptoms.[74,75]

There is an increased risk of morbidity and mortality with common bile duct exploration in patients with CLD,[76,77] with mortality rates as high as 30–50%.[21,77–79] As a result, endoscopic management is preferred when a common bile duct stone is clinically suspected in these patients.[62,77,78] Endoscopic biliary sphincterotomy is the method of choice for the treatment of choledocholithiasis in patients without CLD, although it is associated with an overall complication rate of about 10% and a mortality rate of 0.5%.[80,81] The reports on endoscopic sphincterotomy in cirrhotic patients are few, but the reported mortality rate is approximately 15%.[78,82] Endoscopic papillary balloon dilatation without sphincterotomy and removal of common bile duct stones has been described as a safer method in patients with CLD with a lower risk of bleeding[83,84] and has been shown to be suitable for removal of small bile duct stones.[85] With larger stones, methods combining balloon dilatation with mechanical lithotripsy[83] or sphincterotomy are required.[85]

Cholecystitis is a known complication in patients with intact gallbladders following endoscopic biliary sphincterotomy.[86,87] The combination of endoscopic sphincterotomy and laparoscopic cholecystectomy is therefore the safer option for patients with Child-Pugh class A and B cirrhosis with GS and common bile duct stones.

SYMPTOMATIC GALLSTONE DISEASE IN PATIENTS WITH CHILD-PUGH CLASS C CHRONIC LIVER DISEASE

Patients with advanced liver disease continue to be at risk of excessive mortality and morbidity rates following surgery despite advances in surgery, anesthesia, management of coagulopathy, and intensive care.[88] Compared with patients with compensated liver disease, these patients are more prone to acute liver failure, severe coagulopathy, encephalopathy, adult respiratory distress syndrome, acute renal failure, and sepsis.[88] The degree of malnutrition, control of ascites, level of encephalopathy, prothrombin time, concentration of serum albumin, and concentration of serum bilirubin predict the risk of complications and death after surgery. Other determinants of adverse outcomes include emergency surgery and the presence of portal hypertension.[88,89] Therefore, despite the lack of definitive clinical trials, a more conservative approach seems preferable for patients with Child-Pugh class C cirrhosis and symptomatic GS.[61,62]

Portal hypertension predisposes the patient to variceal hemorrhage, hepatorenal syndrome, hepatopulmonary syndrome, and uncontrolled ascites.[88] During the past 15 years, the transjugular intrahepatic portosystemic shunt (TIPS) procedure has become a safe and effective treatment of portal hypertension.[90] TIPS, however, is most effective and safest when placed in patients with preserved hepatocellular function.[88] Child-Pugh class C CLD is a factor that predicts high mortality rates for this procedure.[90,91] A switch to decompressive surgical shunt procedures is the obvious choice if TIPS fails to control patients with recurrent variceal bleeding.[92]This, too, is only an option in the well-compensated CLD patient with a low operative risk.[92] In addition to expert radiologic and endoscopic facilities, such a patient needs the input of a hepatologist, if preoperative optimization is to be achieved. In such a multidisciplinary team anesthetic support, ability to monitor and control coagulopathy are required to address the common features of advanced liver disease with a view to reducing complications and mortality after surgery.[88,93]

A partial cholecystectomy, performed either laparoscopically or via open technique, has occasionally been recommended in the Child-Pugh class C CLD patient, but the available reports have not used controls.[94,95] A larger experience supports the use of endoscopic retrograde cholangiopancreatography (ERC) in those high-risk patients who present with biliary obstruction. Endoscopic drainage of the gallbladder has been added in some cases but remains an uncommon procedure.[74,75] Alternatively, percutaneous cholecystostomy may reverse the progression of inflammation in patients with cholecystitis and often provides symptomatic relief.[96] Percutaneous cholecystostomy is a radiologic procedure that requires only local anesthesia and could be carried out in an Intensive Therapy Unit setting.[97–99] It allows immediate decompression of the acutely inflamed gallbladder and can serve as a temporizing measure or as a definitive treatment.[97] However, in the presence of portal hypertension and/or ascites, its use is associated with hemorrhage or sepsis. Therefore, there remains a debate as to whether the transhepatic or the transperitoneal route is preferable.[100] A Child-Pugh class C CLD patient who presents with acute cholecystitis and patients with severe CLD who are hospitalized for management of their disease and develop acute cholecystitis during their hospital stay are two distinct groups of patients who benefit from percutaneous cholecystostomy.[98] In the presence of GS disease, recurrent cholecystitis can be as frequent as 25–30% after removal of the cholecystostomy tube.[101,102] Percutaneous GS removal or optimization of the patient where possible, followed by elective laparoscopic cholecystectomy if indicated, is therefore advisable.[97,98] These patients are best managed in hepatobiliary centers where highly specialized hepatologic, radiologic, anesthetic, surgical, and intensive care facilities are available.

CONCLUSIONS

The frequency of GS in patients with CLD is greater than that in noncirrhotic patients and increases with disease severity. Pigment stones seem to be more common in CLD, occurring in up to 80% of cases. Like in the noncirrhotic patient, the vast majority of GS in CLD remain asymptomatic.

Asymptomatic GS and incidental GS, discovered at the time of an abdominal surgery for another cause, in CLD are best managed nonoperatively with close follow-up and early therapeutic intervention if biliary symptoms do occur. The treatment of choice for bile duct stones is ERC, because surgical exploration of the common bile duct has been associated with an unacceptable morbidity and mortality. The treatment of Child-Pugh class A and B patients with

symptomatic cholelithiasis is best done by the laparoscopic method after optimization of the patient. Laparoscopic cholecystectomy is the treatment of choice in the liver transplant candidate, with its associated fewer postoperative adhesions and rapid recuperation. The treatment of symptomatic GS in potential liver transplant recipients is, however, best done after direct consultation with regional hepatobiliary and transplant units.

The treatment of symptomatic cholelithiasis in a Child-Pugh class C cirrhotic patient needs to be approached with caution, because evidence has shown a high rate of morbidity and mortality in this group of patients, even in specialized liver units. For these reasons, such patients are best managed in units that have facilities and the necessary expertise with regard to endoscopic, radiologic, hepatologic, anesthetic, and surgical options.

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Rectal Impaction With Epoxy Resin: A Case Report

Anil K. Hemandas, F.R.C.S.(Ed), Guy W. Muller, F.R.C.S.I., Ibrahim Ahmed, F.R.C.S. (Eng), F.R.C.S.(Gen. Surg)

We describe a unique case of a patient presenting with rectal impaction following self-administration of a liquid used as masonry adhesive for anal sexual gratification. The solidified matter required laparotomy for its removal. Strategies for removing rectal foreign bodies are discussed as well as other consequences of inserting foreign material per rectum. (J GASTROINTEST SURG 2005;9:747–749) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Foreign body, rectal impaction, epoxy resin

Since the early days of medical journalism, reports describing the complications caused by the insertion of foreign objects into the rectum for sexual stimulation have been numerous. An exhaustive list of substances used for anal erotic enjoyment would include animal, vegetable or mineral materials in a liquid, solid or gaseous state. Patients presenting with rectal foreign bodies are predominantly men.

We report an unusual case of rectal impaction resulting from the deliberate injection of a type of glue for sexual pleasure. We believe this to be the first reported case of the unaided insertion of an adhesive material into the rectum for erotic stimulation. A discussion of the use and abuse of enemas and various methods of removal of rectal foreign bodies follows.

CASE REPORT

A 27-year-old unemployed young man presented with lower abdominal discomfort following injection of a liquid adhesive per rectum 5 hours previously. He injected the viscous liquids into his rectum via a dual-chambered glue gun, resulting in an instantaneous exothermic reaction that caused the mixture to solidify and become fixed internally. He had no previous history of bowel disorder or psychiatric disturbance. The patient admitted he had done this for anal erotic enjoyment. The apparatus was examined carefully, but apart from a company name and a product code number, there was no clue as to what chemical had been present in the dual-chambered gun. A general Internet search using just the company name and the product code number was performed. This led us to an exact photograph of the glue gun and a precise description of the adhesive. The product contained 330 ml of epoxyacrylate resin. The resin was supplied as a dual cartridge, which, in addition contained dibenzoyl peroxide and styrene. Final mixing of the chemicals occurs in the nozzle upon squeezing the applicator gun trigger, discharging both chambers simultaneously. It is meant for use in the building and construction trade as a masonry adhesive.

On examination the patient looked well. His vital signs, including temperature, pulse and blood pressure, were normal. There was minimal lower abdominal tenderness but no distension or palpable masses. On rectal examination, a rock-solid foreign body was both visible and palpable just inside the anal sphincter. A plain abdominal x-ray showed a radiopaque foreign object following the exact contour of the rectum stretching from the anal canal to the rectosigmoid junction (Fig. 1). There was no obvious dilatation of bowel loops and no sign of free intraabdominal gas.

From the Department of Surgery, Medway Maritime Hospital, Windmill Road, Gillingham, United Kingdom.
Reprint requests: Ibrahim Ahmed, F.R.C.S., Department of Surgery, Level 3, Medway Maritime Hospital, Gillingham, Kent ME7 5NY, United Kingdom. e-mail: IBRAHIMAHMED07@aol.com

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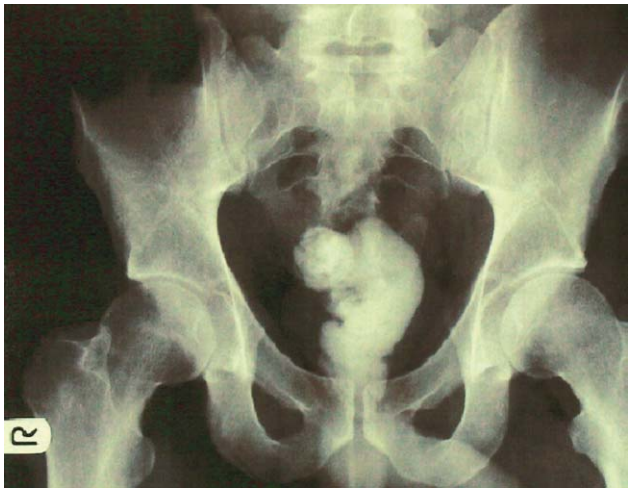

Fig. 1. Plain abdominal-radiograph showing the impacted material.

Advice was sought by telephone from the National Poisons Information Service at Guy's & St Thomas' Hospital, London. They reported that systemic effects from these chemicals were unlikely, but local chemical and thermal irritation was very possible. Additionally, full-thickness erosion was also a potential hazard. It was suggested that oily enemas might be useful in dislodging the solidified epoxy resin. As the masonry adhesive had molded itself to the contour of the rectum extending for a considerable length (about 16 cm) and caused complete blockage of the lumen, conservative treatment was not an option. The decision was made to take the patient to the operating room and attempt removal of the foreign body under general anesthesia. The patient was aware of the possibility of the need to proceed to laparotomy and colostomy to remove the foreign body. It was not possible to mobilize the foreign body transanally. Therefore, the abdomen was opened through a lower midline incision. With gentle manipulation of the rectosigmoid junction, it was possible to deliver the rock-hard material through the anus along with copious mucus discharge and a small amount of blood. The rectal wall was intact with no leaks as confirmed by air and water tests. Sigmoidoscopy showed edematous and inflamed rectal mucosa. Bearing in mind the possibility of full thickness "burn" of the rectal wall and potential risk of later perforation, a loop sigmoid colostomy was raised in the left iliac fossa and the abdomen was closed. Examination of the specimen revealed a perfect stony cast of the rectum, 16 cm long and 300 g in weight (Fig. 2). Grooves in the mass were consistent with rectal mucosal folds.

The patient made an uneventful recovery. Psychiatric counseling was offered to the patient, but he declined. Flexible sigmoidoscopy 6 weeks later revealed normal and healthy mucosa with no strictures. The stoma was reversed without complication.

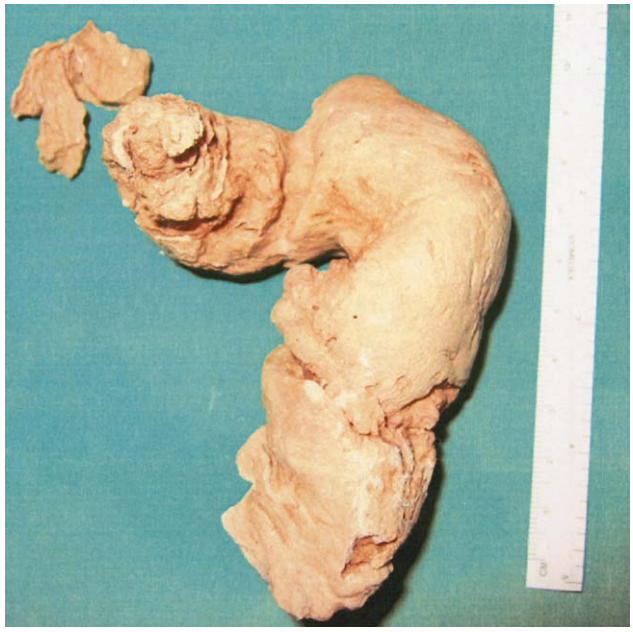

Fig. 2. Specimen after extraction from the rectum.

DISCUSSION

The introduction of foreign bodies into the rectum is not uncommon in medical literature. Objects can be inserted into the rectum for diagnostic or therapeutic purposes, for self-treatment of symptomatic anorectal disease, for sexual erotic activity, by criminal assault, or by accidental occurrence.

The list of objects used for criminal or sexual purposes is exhaustive and is growing. About half of these retained objects tend to be designed originally for the purpose of rectal stimulation, such as toy phalluses or vibrators. The diagnosis is usually easy to establish from the history and a physical examination aided by radiology.

Enemas are mainly used in medicine for diagnostic or therapeutic purposes. Their use as a source of sexual gratification has also been known for a considerable period. The term "klismaphilia" was coined by Denko in 1973 for subjects who used enemas as the primary agents for seeking sexual pleasure.[1] Enemas can induce pleasure by causing mechanical distension of rectum by gas or liquid, which then causes stimulation of nerve endings supplying pelvic organs. Additionally, chemicals can induce pleasurable experiences by causing irritation and rapid absorption. Various solutions are used, including plain water, soap suds, coffee, yogurt, and alcoholic beverages. Drugs used

for this purpose include mainly sedatives and hypnotics.

The use of enemas is not without danger and the consequences of excessive use can even be life threatening. Complications may include impaction, mechanical trauma, infection, hemorrhage, chemical colitis, anaphylactic reactions, embolism, and, in the longer term, formation of strictures. In extreme circumstances, major complications can occur such as complete large bowel obstruction and perforation with possible progression to fecal peritonitis.[2–5]

A useful classification of rectal foreign bodies is based on the extent of injury caused and includes four categories, with category one being retained foreign body causing no injury, category two causing nonperforative mucosal laceration, and categories three and four representing sphincter injury and rectosigmoid perforation.[6] Alternatively, they can be classified as high-lying or low-lying to help with the initial approach to the problem and in formulating an ultimate treatment plan.[7]

With adequate sedative relaxation aided by local anesthetic, transanal removal in the emergency department may be feasible for most types of foreign bodies in the rectum, avoiding laparotomy.[8] This applies more so to the majority of objects in the lower or mid-rectum up to a level of 10 cm. The conscious patient may be able to assist with a Valsalva maneuver. Sometimes spinal or general anesthesia becomes necessary because of pronounced muscle spasm and significant patient discomfort. Those in the upper rectum may require laparotomy for retrieval.[9] This offers the additional advantage of transabdominal manipulation to aid transanal recovery of an impacted foreign body. Occasionally, colotomy has been performed for removal.[10] Recently, some foreign bodies have been successfully removed endoscopically using novel methods.[11]

A Medline search from 1966 to the present showed only one paper describing a scenario similar to ours. Stephens and Taff, in 1987, presented a patient who was voluntarily given a concrete enema that was introduced by his sexual partner.[12] Removal required a general anesthetic and anal dilatation. Transanal delivery of the solidified concrete mix was then possible without abdominal surgery. The appearance of the rectal mucosa was hyperemic and edematous on visualization with a sigmoidoscope. There were no persisting injuries to the bowel in the long term. Through this search we realized that ours was a unique case, and we believe that it is the first reported case of the unaided insertion of an epoxy resin adhesive into the rectum for anal erotic stimulation.

As in the aforementioned case, we attempted to remove the hardened resin through the rectum by digital manipulation aided by oily enemas. Since the foreign body had molded itself so well to the contours of the rectum, all the options that were attempted for nonoperative removal failed. To prevent any further trauma to the rectal mucosa, progression to laparotomy was necessary. We considered that formation of a temporary diverting colostomy was the safest management plan to allow healing to occur and to reduce the potential complications of late perforation.

We stress the potential danger created by manufacturers who produce hazardous materials but fail to label the product with details of their contents. Additionally, health warnings or advice printed directly on the external casing may speed diagnosis and treatment in the event of a medical emergency. It may even prove to be life saving. In this case, we were able to discover the chemical composition of the substance via the Internet, and base our management plan on that information.

As the exploration of anal eroticism increases in popularity, more and more cases of complications as a direct result of their abuse are likely to be encountered. Ingenuity and patience are advocated in attempting their removal. Patients should be offered psychosocial counseling.

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