Introduction of Dr. Carlos Pellegrini

Prof. John Wong

As Vice President of The Society for Surgery of the Alimentary Tract, I am honored to introduce Dr. Carlos Pellegrini who will deliver the presidential address. The office of President of The Society for Surgery of the Alimentary Tract has always been held by a very distinguished member. Notwithstanding talent and effort, the road to the presidency is not an easy one. In the case of the Fortieth President, Carlos Alberto Pellegrini, it has been a long, winding, and difficult road, with Dr. Pellegrini having to prove his worth on matters most take for granted.

Dr. Pellegrini was born in a small farm community of about 400 people in Argentina. Both of his parents, as well as his maternal grandparents, were physicians. As a small child he accompanied his parents on home visits. It was from those visits that he developed an interest in becoming a doctor—more in the concept of helping needy human beings than anything else, although being paid in farm animals and produce must have been captivating. In his childhood, he also learned to take care of beehives and manage some unfriendly bees—skills that served him well with the advent of the HMO, as well as when he was the chairman of a department of surgery.

Dr. Pellegrini's love and respect for his parents were profound, and leaving Argentina for the United States caused him deep emotional anguish. His mother passed away recently, leaving a permanent gap in his life. For Dr. Pellegrini, however, the knowledge that he gave her the joy and the satisfaction of seeing her son successful, and that he had touched the lives of many individuals, help to ease the pain of separation and loss. His relationship with his father is no less strong. The affection and admiration Dr. Pellegrini holds for him was extraordinarily intense.

Although it seemed natural that Dr. Pellegrini would become a doctor, the reason for choosing surgery was somewhat different. He "fell in love with surgery" during his first year of medical school in Argentina because of an inspiring anatomy teacher; for the rest of his medical school years he taught gross anatomy and began assisting in the operating room. During his last year, he met Professor Juan Miguel Acosta (of biliary pancreatitis fame) (Fig. 1), and I suspect Dr. Pellegrini was one of the workers who sieved through what we might call "raw data" to find the elusive biliary calculi. He went on to complete his surgical residency with Professor Acosta, who is with us this morning together with other distinguished Argentinian surgeons who helped to shape Dr. Pellegrini's career.

As a medical student, and then as a doctor who saw the mounting social and political unrest on a daily basis in Argentina, he was disillusioned and became a student activist trying to help restore order and human rights. For this he was targeted, arrested, and jailed, and very likely is the only president of the Society to have been jailed. After his release, in order to protect himself and to pursue his love of surgery, he made the painful decision to leave his parents and his country. His first job offer was in Saudi Arabia—a place likely to cure him of his activist tendencies. While awaiting his papers to go to Saudi Arabia, through the good offices of Professor Acosta, Dr. David Skinner offered Dr. Pellegrini a temporary job in his laboratory at the University of Chicago. Thus began the life of Dr. Pellegrini in the United States.

Through Dr. Skinner, Dr. Pellegrini met Dr. Tom DeMeester (Fig. 2), a recent past president, and the two of them became the closest of friends. He completed a second residency in Chicago, whereupon Dr. Lawrence Way (Fig. 3), also a past president, offered him a position in 1979, and for the next 15 years they worked together. Dr. DeMeester and Dr. Way were obviously impressed with Dr. Pellegrini's potential; they spent countless hours with him helping him not only with acquiring experience in the regular resident repertoire of clinical and operative care, but also with such mundane skills as writing and speaking English. They also tutored him in the art of clinical research, presenting to audiences, and speaking in public. In sum, Dr. Pellegrini's interest in research in "whole organ physiology" of esophagus, his work in respiratory complications of reflux, and his reputation in the clinical domain, were the product of two outstanding and devoted mentors. His gratitude and his loyalty to them, from his perspective, is no more than is due. Few would have invested such efforts on a South American immigrant activist who was scientifically naive and linguistically immature. But Dr. Pellegrini

Fig. 1

Fig. 2

Fig. 3

Fig. 4

was a good student. He learned from Dr. DeMeester and Dr. Way to be precise, concise, and straightforward. But his own talent led him to be creative and intuitive—always trying to incorporate some new perspective into his work.

In 1993 he accepted the position of Professor and Chairman of the Department of Surgery of the University of Washington in Seattle, with the support and blessing of his Dean at the University of California, San Francisco, Dr. Haile Debas (Fig. 4). And in 1996 he assumed the Henry N. Harkins Chair.

His decision to make the United States his home was not single faceted. Once made, he volunteered in the Armed Forces in order to be more fully integrated into life in the United States, and to show his gratitude to his adopted country. He saw active duty during the Gulf War when he was deployed at Walter Reed Army Medical Center; he was twice awarded the Meritorious Service Medal. When he retired as a Lieutenant Colonel he said, "during those years I met some of the most service-oriented and courageous men and women in this country. This service influenced my life profoundly."

Dr. Pellegrini loves his job. Even now, a patient with a problem can still excite him as when he was a resident. He has that unique human dimension which enables him to relate to the poor and the rich, the sick and the well, the young and the old, patients of all races and backgrounds—all with equality and dignity. He is relaxed with them all, can exchange anecdotes and jokes, and many of his patients remain lifelong friends. He gives generously of his time, and his tolerance also extends to his faculty and his administrative and support staff, and they reciprocate in turn. I know that he depends a great deal on his trusted and able personal assistant, Jean McAllister, who shared some of her secrets with me.

Dr. Pellegrini has had an endless stream of fellows who have gone through his program in San Francisco and in Seattle. But the person he shares a special bond with is Dr. Marco Patti, who took over his activities in San Francisco when he left for Seattle. Dr. Patti also spent several months with me in Hong Kong, and during that time he offered insights into Dr. Pellegrini's engaging personality.

In dealing with difficult situations, Dr. Pellegrini exhibits two traits—one is to tell a riveting story, usually self-mocking, with his favorite saying "you won't believe this story"; the other is to supply food, such as home-cooked pasta, to friends in need. Both techniques produce excellent results. Some of the latter method, that is, the application of food, has clearly been used personally—also with good effect. I understand he has a personal trainer at a health club and plays tennis vigorously, but his love of good food and fine wine appear to have had, for the moment, the upper hand.

Dr. Pellegrini is a friend one wishes to have in life and for life—always there when you need him, and freely giving of his help. For example, at a meeting which I chaired, he intuitively knew when and how to change the direction of a discussion and help bring it to a satisfactory conclusion. Or when a resident would really like to perform a certain operation, even though Dr. Pellegrini might be short of time, he would help the resident to do it. He has taken on more than any one surgeon and chairman can. I would like to cite two of his current assignments—Secretary of the American Surgical Association, and President of the International Society for Digestive Surgery—in addition, of course, to assuming the presidency of The Society for Surgery of the Alimentary Tract. I know he has had to decline other offers of high office so that he could complete the tasks at hand at a level that would do justice to that office and, by extension, do honor to his parents, his mentors, his friends, his family, and his colleagues.

In spite of his accomplishments thus far, I know Dr. Pellegrini has three ambitions left. The first is to build an even better department than he has done so far, the second is to enhance the education of gastrointestinal surgeons in the United States and abroad, and the third is to share his life with Kelly. He will achieve them all.

In closing, I would like to say that in addition to the above characterizations, Dr. Pellegrini also enjoys life. His philosophy is that life and work should be a whole. He can enjoy the best in life as well as very simple pleasures. He treasures every moment. As an Italian law professor once said and which adequately describes Dr. Pellegrini ". . . A real professor teaches with his words, his writings, his life, and here lies his greatness. . . ."

Ladies and gentlemen, members of the Society, I present to you the Fortieth President of The Society for Surgery of the Alimentary Tract, Dr. Carlos Alberto Pellegrini.

SSAT 2000: A Prosperous Society Looks at Its Future

Carlos A. Pellegrini, M.D.

The honor to serve as your president for the past 12 months has been a most humbling and in many ways a most enlightening experience. The very fact that this responsibility was bestowed, for the first time in the history of The Society for Surgery of the Alimentary Tract (SSAT), on a person born and educated in Latin America is both a matter of personal pride and a reflection of the tolerance, warmth, and wealth of opportunities that America provides to its immigrants. It is also a reflection of the influence of many individuals who have played a vital role in my professional development and whose careers and attitudes I have tried to emulate. I have, indeed, been fortunate to work closely with some incredible people: Professor Juan Acosta, whose contributions to the understanding of the pathogenesis of acute pancreatitis stand as a testimony to the fact that limited resources can be overcome with intelligence, hard work, and perseverance; Dr. Tom DeMeester, a former president of the SSAT, whose work has made it possible to understand the intricacies of esophageal physiology and whose leadership in gastroenterology has brought so much respect for surgeons; Dr. Lawrence Way, also a past president of the SSAT, one of the leading surgical gastroenterologists in America, whose legendary and clear-minded writings have enlightened so many surgeons working in the field of hepatobiliary diseases; and Dr. Haile Debas, who has proved that a surgeon can be a leading scientist, an influential educator, and an erudite philosopher. Each one of these giants has helped shape my life by introducing me to the field of clinical investigation, by helping me stand in public and give a talk—albeit with an accent—by reviewing and rewriting my manuscripts or holding my hand in the operating room, and by showing me how to organize and run a department of surgery. To them, and to the many others at the University of California, San Francisco and at the University of Washington, with whom I have been blessed to be associated, thank you. This is a tribute to you.

Now that we have successfully crossed the threshold into the new millennium, apparently overcoming the fear and excitement associated with that transition, I thought it would be important to discuss the role of the SSAT in this new era. I will begin by laying before you our first challenge as presented to us by one of our founders, with an analysis of what I consider the three most outstanding landmarks in the history of the SSAT. The strategic decisions that led to those landmarks have shaped the Society into what it is today, and are the reason for our current prosperity. Because each of these bears so deeply on what we are today, I will also bring you up to date on what we have done this year to further each particular cause. Finally, I want to focus on the challenge we face for the future: What question should we ask ourselves now, and what is the most appropriate answer?

OUR "DECLARATION OF INDEPENDENCE"

The first presidential address read before the SSAT, given by Dr. Robert M. Zollinger during the fourth annual meeting of the Society in Atlantic City on June 16, 1963, was entitled "Justifying our Existence."[1] This was our Declaration of Independence; this was our challenge. Dr. Zollinger said, first, that our existence as a separate and distinct society would be justi-

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fied in so far as our annual programs reflected the entirety of the gastrointestinal tract and not just the colon and rectum as had originally been the case. Second, he advanced the concept that the SSAT should play an important role in research: "While we can justify our existence in trying to evaluate the best operation for some of the more common lesions and to lower the high mortalities of some others, there is also a great need for research in some of the more common problems related to the gastrointestinal tract." He suggested that "if we have encouraged and brought into focus, at the national level, the clinical and experimental solutions to the many problems of the alimentary tract, we will have justified our existence." As I have studied the events that have occurred since Dr. Zollinger's challenge, I have come up with three landmark events that I believe have shaped us into what we are.

MAJOR LANDMARKS OF THE SSAT

From Isolation to Integration

One of the most important developments in our history relates to the emergence of Digestive Disease Week (DDW). This occurred in 1973, when the SSAT met at the same time as the American Gastroenterological Association (AGA) in New York City, and shortly thereafter, DDW as we know it today was born. This monumental change, the details of which were very nicely depicted in Dr. DeMeester's presidential address,[2] from being an isolated society of surgeons to an integrated society of surgical gastroenterologists—an apt term coined by Dr. Andrew Warshaw[3]—marked a defining moment in our history. I am not talking about the financial implications or the sheer number of attendees that would, over the ensuing years, have access to our meetings. Instead I am talking about a change in our mindset, the change from a technique-oriented society to a discipline-oriented society, and the critical positioning of our group so as to influence directly the *entire* (not just the surgical) management of patients with gastrointestinal disease.

In the past few years we have developed this concept of integration even further. Indeed, the symposia with the AGA, American Association for the Study of Liver Diseases (AASLD), and American Society for Gastrointestinal Endoscopy (ASGE) have now become a most important and well-attended part of our annual program. A few years ago we started partnering with the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), inviting them to participate in our annual meeting. This year we invited the American Society of Colon and Rectal Surgeons to organize a new program, which was actually presented yesterday as the opening of the SSAT plenary sessions. Furthermore, our board has continued to work closely with the International Society of Digestive Surgery and with other regional societies exploring common goals and opportunities to work together. I had preliminary meetings with the president and selected members of the board of the American College of Gastroenterology (ACG), and there is enthusiasm to explore some form of a cooperative venture. This year I will be bringing forward to our Board of Trustees a motion to explore a more formal arrangement to participate in the clinical congresses of the ACG for their 2001 meeting and beyond. This, I believe, should further expand upon our unique ability to integrate and thus influence the world of gastroenterology at large.

As this process of mingling with other societies takes place, we must also be concerned about remaining ourselves, about keeping our identity. As with any group concerned about boundaries that define identity, so too has our Society been concerned about boundaries that both include some issues and exclude others. We shall continue to work this fine line of integrating to influence the process while remaining who we are. Cardinal to this point is the second major landmark in our history: the change in the composition of our Society resulting from a change in the philosophy of membership in our Society.

An Expanded Membership

Dr. Bernard Langer introduced the concept of expanding our membership at a board meeting in 1993.[4] The idea of this expansion was that the SSAT should truly represent those practitioners who actually delivered the gastrointestinal surgical care. Questions of membership have provided an ongoing and evolving dialectic over the years. If, on the one hand, we open membership too broadly, we become indistinguishable from the many other societies who do much the same kind of work as our members, and we lose our identity. If, on the other hand, we define ourselves too narrowly, we risk the righteous animosity of those who find themselves on the outside looking in.

Adopting this new policy was not easy. It meant changing from an elite group of university-based gastrointestinal surgeons to a "broadly based organization representing the whole spectrum of surgeons whose major interest is gastrointestinal and abdominal diseases."[5] But, with Dr. DeMeester and Dr. Way as presidents of the Society and Dr. Robert Beart as chair of the membership committee championing this idea, the change took place. The SSAT more than doubled its membership, and today we have more than 2000 active members.

What do we look like now? The survey conducted last year showed that 50% of our members have a full-time appointment in an academic practice, and of the remaining members, the majority have a clinical appointment at an academic center. Our members overall spend 70% of their professional time in clinical practice and of this time, more than half is spent in the area of surgical gastroenterology. In that sense, the profile and character of the membership continue to reflect the mission of our Society.

A new challenge, as a result of the liberalization of our membership requirements, is that we are now attracting a younger generation with different needs and different views than our traditional members. Many of these individuals are eager to participate in the affairs of the Society at a much earlier age than we did. Many of these individuals are still looking for further training opportunities in research and in clinical practice. It is imperative that we address the needs of this new generation if we intend to continue to exist as a vibrant society. With that in mind, we enlarged some of our committees and appointed this young and energetic new blood to their ranks. We also appointed a bylaws committee to look into our governance and committee structure so that appropriate recommendations for change may come forward to our board. We asked the Patient Care Committee to take on the task of redesigning our website, to make it more functional and more interactive, and thanks to the extraordinary efforts of Dr. William Traverso and the members of this committee we have just unveiled our new site. This young generation told us they prefer electronic communications, so an electronic media committee will be created this year to continue the work begun by Dr. Traverso and his group. We discontinued the newsletter as we heard that our members did not find it useful, and instead will carry out all of our communications through the web. Thus we are responding to the needs of a younger generation.

The Creation of a Journal

The third landmark, the creation of our own journal, was likewise a rather difficult and lengthy process. Almost since its inception, and in part because of the strong influence of Dr. Robert Zollinger, then the editor of the *American Journal of Surgery*, the Society established a very close relationship with this journal. In 1995, the Board of Trustees decided to establish a journal owned and copyrighted by the SSAT: THE JOURNAL OF GASTROINTESTINAL SURGERY. The Board also decided that two prominent past presidents of the Society, Dr. John Cameron and Dr. Keith Kelly, were to jointly run the journal as co-editors. The journal saw the light of day in 1997, and within two years was recognized by *Index Medicus*. We are now in the fourth consecutive year of publication of the journal and it has been a success from every point of view. It is a beautifully designed and produced journal. It is a natural vehicle for dissemination of knowledge in our discipline and an important resource for the students of gastrointestinal surgery. But more than this, it gives the SSAT a clear identity, and it recognizes gastrointestinal surgery as a separate and distinct discipline emerging from the broader field of general surgery. In the survey conducted in 1999, three quarters of our membership identified the journal as the most important of the publications from the Society, and three quarters also indicated they were very satisfied with the journal as it is currently produced.

It was not surprising, therefore, as we approached the fifth year of our publication and the end of our original contract with Quality Medical Publishing, that we received an overwhelming and enthusiastic response from every major North American and European publisher to our request for proposal. This year the Board received a formal request from the American Hepato-Pancreato-Biliary Association to publish its papers in the journal and our Board of Trustees has decided, in principle, to accept this request. There is no question that our journal is well established. We owe Drs. John Cameron and Keith Kelly a tremendous debt of gratitude for making this such a success.

Thus, as we enter this new century, I believe we have lived up to our first challenge and "justified our existence." In fact, I believe we have much to be proud of in that we—you—have exceeded most of the expectations of our founders as expressed in Dr. Zollinger's address.

We have, indeed, become a prosperous society. But, as we look into the future, we need to ask once more: What is the reason now for our continued existence? The SSAT is now in a radically different environment from what existed 38 years ago. We have integrated with many other societies, and by so doing we have positioned ourselves so as to exercise significant influence. We have attracted a unique cadre of individuals who are the elite and most respected practitioners of surgical gastroenterology. We have now incorporated a new breed of young, energetic, and enthusiastic individuals, and we have our own independent voice through the journal. We have assumed a social responsibility and we are expected to deliver in kind. In this new environment we need to revisit the question of what justifies our existence.

I believe we can address this question by setting forth a unifying theme, or common thread, that can

integrate all our achievements and reinterpret them for the new era. I draw your attention to the Society's fourfold mission statement, from which we can derive this renewed thrust. Our mission statement defines the goals of the SSAT as follows: "To stimulate, foster, and provide surgical leadership in the art and science of patient care; teach and research the diseases and functions of the alimentary tract; provide a forum for the presentation of such knowledge; and encourage training opportunities, funding, and scientific publications supporting the foregoing activities." With one exception we have achieved these goals. The one area that can provide the continuity, the common thread that takes us through the new decade, is the issue of training. Attention to training, I believe, will make use of our integration with other societies and thus our ability to influence the process. A focus on training responds to the needs of a broader and younger membership, and responds to the public's request for specialized care.

OUR ROLE IN THE TRAINING OF SURGICAL GASTROENTEROLOGISTS

Since this is not a new issue, I could spend part of my remaining time with you reviewing the experience of the past in regard to how our society should or should not address the question of specialized training in gastrointestinal surgery. I could, in other words, lay down a trail that we have created and followed in the past, which might seem to lead in a certain direction for the future. Instead, let me play the role of expedition scout, striking out into relatively unexplored territory. I would propose that we look afresh at the idea of a training fellowship for surgery of the alimentary tract, to see the idea on its own merits, in innocence, as it were, of the possible obstacles.

In particular, I want to discuss what I think the public expects from The Society for Surgery of the Alimentary Tract, I want to highlight what the residents finishing general surgery training perceive that they need, I want to emphasize what our new expanded membership expects from us in this regard, I want to discuss what might happen if we ignore this issue, and I want to propose a solution. What I suggest is that we tune our ears differently, so that we might correctly interpret the signs of coming change. If we are willing to do that, we will be in a position to influence the parameters of change, rather than being taken unawares. If we correctly extrapolate from the current scene in gastrointestinal surgery, we can position ourselves appropriately so as to fit in with the overall surgical scene, and not seem to be fighting against our own. If knowledge is control, foreknowledge is leverage.

The Public's Expectations

The American public today is much better informed than it was only a few years ago. The average individual now has access to the latest information, and thus seeks more and more specialized care. This level of sophistication is perhaps, as Dr. Joe Fisher very nicely pointed out in his recent article in the *Bulletin of the American College of Surgeons*, the main reason for the failure of the feared expansion of managed care, and of the concept of "generalism" that was so preeminent in the early 1990s. Speaking of the choice the public makes when seeking care, Dr. Fisher said, "Once they are diagnosed with a serious illness, or they perceive themselves to be seriously ill, the public wants their care to be administered by a specialist—and not just any specialist, but a well-trained specialist."[6] The American people now want direct and unimpeded access to individuals who have the expertise to solve their problems. They demand competence, and the best assurance of competence is thorough and complete training. This is true today, even more so than five years ago. Just think of the profound impact that the Institute of Medicine report "To err is human," released last November, had on our congressional leaders, the public, and the profession. The report revealed that the estimated number of annual medical errors which led to adverse medical outcomes ranged from 49,000 to 98,000.[7] Insufficient training in technical surgical and procedural skills was one of numerous root causes cited, a cause amenable to improvement by training. Our Society should look at this report as a challenge that is also an opportunity.

Other organizations have reacted positively to these societal changes. For example, the American Board of Surgery recently created a sub-board in vascular surgery, recognized surgical oncology as a distinct discipline, and focused on the issue of competence. These are but a few illustrations of how the American Board of Surgery has evolved in their thinking to adapt to the societal pressures outlined above.

Fellowship Training and Expectations of Surgical Residents

What do our residents and young members expect? As we look around us, we can see that formal postresidency training has become the paradigm used by almost every other discipline in America today. In fact, it would be impossible to imagine any other viable training scheme today. The postresidency training paradigm works in all the other disciplines, and there is no evidence that it cannot work in ours. The results are obvious as we look at the surgical scene in this country. The availability of such formal training op-

portunities in a defined area of surgery captures the imaginations, and therefore the enthusiasm, of the best minds. The existence of approved fellowships fosters growth in the various disciplines—as we have seen in vascular surgery, and more recently, surgical oncology. In the M.D. Anderson and Sloan-Kettering fellowship programs, 80% of those who finish their training there stay in academic medicine. The point is, such high-quality fellowships attract high-quality surgeons, and these bright people remain committed to the discipline and to academic surgery. Furthermore, there is a powerful multiplying effect; those who emerge from such training are the trainers of future surgeons, and the pool in that discipline is thus enriched. As chairs look to recruit new surgical oncologists, they look first, and primarily, to the graduates of those programs. The same is true for transplantation and other disciplines; in all cases a uniquely qualified cadre of surgeons is the outcome.

It is clear that residents speak with their feet: of the 1995 graduates of accredited surgical residency programs, 446 or approximately 44% were identified during 1996 and 1997 in one of six Accreditation Council for Graduate Medical Education (ACGME)–approved fellowship programs (colon and rectal, plastic, surgical critical care, pediatric, vascular, and cardiothoracic) as reported by Bland.[8] In the most recent longitudinal study of surgical residents in the United States, Kwakwa and Jonasson[9] noted that nearly half of the residents who graduated during that study period chose to enter a fellowship program. And, in the most current survey available, Rattner et al.[10] found that 60% of current residents at the postgraduate year 4 or 5 level were considering a fellowship on completion of their residency training.

Residents seek further training at the completion of their residency for a variety of reasons. First, as Dr. Way pointed out in his presidential address,[11] acquiring the necessary skills to become competent in the use of complex technology, now a common theme in all disciplines, requires a level of exposure to this technology that can hardly be acquired in the process of a "general training."

Second, general surgery training exposes the residents, appropriately so, to experience in nine primary components and three secondary components of surgery. General surgery residency training in this country is excellent and unparalleled. For example, the most current data from the Residency Review Committee (RRC) on 880 residents graduating in 1999 show that, on average, chief residents had done 948 operations as surgeons. Among them, they had done 74 breast operations, 104 biliary tract operations, 88 herniorrhaphies, 31 appendectomies, and 43 colectomies.[12] These operations comprise the bulk of general surgery as reported by Dr. Ritchie at last year's meeting of the American Surgical Association.[13]

However, as good as our residency system is to prepare residents for the practice of general surgery, focused experience in complex gastrointestinal surgery is, appropriately so, not emphasized. For example, the 1999 graduating residents had, as an average, performed one total esophagectomy, one total gastrectomy, four laparoscopic antireflux procedures, three liver resections, and so on.[12]

Thus those residents who do not want to practice as general surgeons in an average community hospital or in rural areas seek additional training. As they do so, they find opportunities for formal (i.e., ACGME approved or Society supervised) training in most disciplines. Today these include surgical oncology and transplantation, two disciplines that have significant overlap with gastrointestinal surgery. Obviously these disciplines are recruiting individuals who might, had the opportunity been there, have chosen to become surgical gastroenterologists. What is even more interesting is that these formal opportunities for postresidency training exist in colon and rectal surgery, an area of the alimentary tract that is no more complex than the esophagogastric, hepatobiliary, and pancreatic areas. It is totally perplexing that in this current environment, the only areas for which there is no formal training (ACGME approved or Society supervised) is for esophagogastric and hepatobiliary and pancreatic surgery.

The Consequence of Inaction

With this state of affairs, two important problems emerge. First, other disciplines are creating specialists who are slowly but surely taking over the traditional field of interest of surgical gastroenterologists. Liver resections and complex hepatobiliary reconstructions are now routinely performed by transplant surgeons who have received the appropriate training and exposure to surgery of the liver. Gastric and pancreatic cancers are increasingly becoming part of the field of the surgical oncologist, and esophageal resections are carried out by thoracic surgeons. The emphasis of these specialties—whether it be immunosuppression, cancer cell biology, or cardiac physiology—is certainly not the physiology and pathophysiology of the alimentary tract. Yet because their training has given them the technical expertise needed to perform the operation, they do it. Emphasis on technique alone places the surgeon in a dependency position with respect to our medicine colleagues. If this trend continues, we will have less and less surgical gastroenterol-

ogy; we will have essentially been replaced. And just imagine, even if for a second, the impact that all of this is having on the very existence of the SSAT.

Second, and along the same line of technique over discipline, we have seen a recent proliferation of informal, unsanctioned fellowships, many of which emphasize the application of minimally invasive techniques to the treatment of gastrointestinal disease. These arise for one reason: They are needed, and there is nothing in place that will officially satisfy that need. This situation may well achieve the dreaded fragmentation of the discipline of surgery; if it continues, there will be a patchwork of programs acting as mavericks in an unmonitored environment. The potential is there to cause greater harm than benefit to surgery and to patients. Like any unwelcome or unappealing concept, we have the choice whether to acknowledge its existence or ignore it. If we ignore it, it can become dangerous or at best distracting. If we acknowledge it, we can then consider how to manage it. If we manage the phenomenon of mushrooming informal training fellowships, those that are substandard will fall away, and the quality of the discipline will be upheld and improved.

A Potential Solution

What should be the role of the SSAT in the development of postresidency training for the areas of the alimentary tract that are currently neglected?

The issue of clinical training has been discussed in the past by Dr. Jaffe and others, but was really brought to the forefront by Dr. Cameron in 1992 in his presidential address entitled "Is fellowship training in alimentary tract surgery necessary?"[14] At that time he argued that the availability of focused, postresidency training in other primary components of surgery has "stimulated the interest of young individuals entering surgery." He pointed out the substantial motivation toward scholarly activity that such an experience fosters, and the resulting benefit to the care of patients. Furthermore, he showed that 70% of the 157 program directors of general surgery training programs who responded to his survey believed that such a fellowship would make gastrointestinal surgery a more attractive area to finishing residents, 75% believed such training opportunities were desirable, and 75% believed that the SSAT should oversee them.

In 1995, President Langer charged me as the chairman of the newly constituted education committee with the task of crafting a new training opportunity in the form of a fellowship for gastrointestinal surgeons. Our committee presented a carefully crafted and comprehensive proposal for a gastrointestinal fellowship in 1996. The structure of the fellowship was based on that of current RRC-approved fellowships. The design of the accreditation process was based on the one that the Society of Surgical Oncology and the American Association of Transplant Surgeons currently use to accredit their fellowships.

On that basic concept, and recognizing that colon and rectal fellowships already existed, and were indeed—and paradoxically—ACGME approved and regulated, we developed a fellowship with two components: one with a focus on hepatic, biliary, and pancreatic diseases and one with a focus on esophagogastric pathology. Both of these components included extensive exposure to other appropriate disciplines: interventional radiology, endoscopy, and gastrointestinal physiology. Both provided extensive exposure to minimally invasive techniques, and both viewed the fellow as the center of a multidisciplinary educational and research effort.

Thus, as you can see, a considerable amount of work has been done. This work has led to identification of the areas of surgical gastroenterology for which currently there is no formal training opportunity. The framework of what that fellowship might look like and the process by which such fellowships might be accredited has also been set. Our education committee, under the leadership of Dr. John Hunter, is currently compiling a list of existing training opportunities so that we may post them on our website in the near future. This is an "all-inclusive" list that is intended only to provide contacts for residents seeking postresidency training. Although it is far from the ideal fellowship described above, it represents work done in conjunction with SAGES. I would propose that, starting with our latest draft, we use our unique ability to integrate with other societies to determine which might be the ideal fellowship that we need to produce the leaders of tomorrow. To this end, I will ask our board this coming year to take the lead in the formation of an educational council comprising members from other societies such as SAGES and the American Hepato-Pancreato-Biliary Association, both of which are interested, and both of which have developed their own version of postresidency training. I believe this kind of cooperative effort is essential if we are to avoid the very understandable concern that advanced training fellowships are likely to further fragment the discipline of surgery. Far from fragmenting surgery, an educational council can work to find ways that the different societies can complement and support each other, so that in the end patients get the quality of service and care they are increasingly demanding. In fact, such an effort can perhaps avoid a particular kind of fragmentation that can occur when

we look only at training surgeons in specific techniques, as opposed to training them in a particular discipline. Certainly fellows must receive technical training, but I believe that training needs to be seen in the context of the discipline, so that we create experts in disease management, not just operators, and by doing so, we expand the role of the surgeon to encompass the total management of the patient with gastrointestinal problems.

In an intersociety council, we may be able to provide this unique opportunity to our candidate members, and to the next generation of surgical residents in this country.

I believe that the time has come to develop, in a responsible, mature, cooperative, and amicable way, the next version of the fellowship in alimentary tract surgery. The idea would be to build on the comprehensive program we developed, to set the appropriate rules and a meaningful oversight process so that we can identify tertiary care centers in this country that can withstand the scrutiny of an appropriate certification process and become approved sites for fellowship training. These places would have to provide not only the appropriate number of cases but, more important, the appropriate environment for adequate interactions and training of the fellow in surgery of the foregut.

If we do this, I believe we will fulfill the mandate that we received from our founders, I believe that with this we will have carried out our social contract, and I believe we will have justified our existence in the years ahead.

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Remarks on Accepting the SSAT Founders Medal

*Paul H. Jordan, Jr., M.D.**

First and foremost, I want the membership to know how deeply honored I am by the presentation of the Founders Medal. I greatly appreciate this award because of my great respect for the Society. I have watched it mature for nearly 40 years since its beginning as the Society of Surgery of the Colon. I would like to comment on the reasons we have to be proud of The Society for Surgery of the Alimentary Tract.

When I made application in 1963, I did not recognize the need for the organization. I was one of those who asked, "Why another surgical society?" At the time the name was changed to The Society for Surgery of the Alimentary Tract (SSAT), anyone who could wield a knife considered the gastrointestinal tract fair game. All of the abdominal organs could easily be exposed and operated on. Drs. Turell, Cole, and Waugh, the founding fathers, correctly recognized the need for an organization that would lead the way in education and research pertaining to gastrointestinal surgery. But it did not come easily.

The first meetings were held in the summer of 1960, in conjunction with a meeting of the American Medical Association. I presented a paper at the fourth meeting in Atlantic City on the physiology of bile, perhaps an untimely subject to attract an audience of surgeons.

The meeting was held in a small room. Although probably an exaggeration, Dr. Harwell Wilson estimated that approximately 60 people were in attendance including Drs. Bob Turell, Claude Welch, Sir John Bruce, Jonathan Roads, Warren Cole, and Robert Zollinger, the chairman.

It was recognized that to attract surgeons, it would be necessary to have a program where members presented their best work. I remember vividly Dr. Frank Moody fretting about how to cajole the members to support the meeting in this way. It was eventually accomplished in spite of disapproval of the Society by some. Our program is strong, even attracting presentations from members of organizations where the gastrointestinal tract is on the periphery. Papers presented at our meetings have one of the widest audiences in the world.

Needless to say, there were many trials and tribulations before the SSAT achieved its current status. As one reflects, we are greatly indebted to those early leaders whose courage and fortitude permitted them to champion what they believed in. We can be proud of a great surgical organization and can give thanks to those who had the wisdom to found it, and to those who made sure it survived and did not fail. We did need another surgical organization!

The objectives of the Society remained narrowly focused until 1978 when Dr. Bob Zeppa encouraged us to become a part of Digestive Disease Week. The idea of a liaison with our medical counterparts was previously raised by Drs. Loyd Nyhus and Henry Harkins in 1966. There was considerable disagreement regarding such a move as well as paranoia as to whether we would be disenfranchised by a more powerful organization. There is now agreement that it was a very important decision to have made. Our ability to fraternize with others interested in gastroenterology has been an invaluable learning opportunity.

For a long time there were discussions about the wisdom of sponsoring a postgraduate course. The thought prevailed that there was already one postgraduate course, so why did we need another? The idea of a postgraduate course coincided with Dr. Turell's idea that The Society for Surgery of the Alimentary Tract should have educational and research arms. Finally, the postgraduate course was adopted. There is no doubt that the need for and advantages of such a course are great, as can be attested to by the course just concluded. The Society for Surgery of the Alimentary Tract has from the beginning considered research and teaching its main responsibilities. These objectives have been fostered not only by our annual meeting and the postgraduate course but also by the resident research conference and the career development award program. Because of restricted funds for research from other sources, our efforts in these ventures are important to our national interest. To paraphrase Dr. Jim Thompson—It is our Society's contribution to prevent the medicine of yesterday remaining the medicine of today.

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So, by slow cautious steps, our Society has fulfilled many objectives. In spite of preexisting concerns, its most recent accomplishment was the establishment of an official journal devoted entirely to gastrointestinal surgery, the JOURNAL OF GASTROINTESTINAL SURGERY. This venture is off to a grand start, but to maintain its momentum its editors will need the support that our membership has generously given to previous teaching, education, and research endeavors.

Finally, our Society is strengthened by its decision to follow Dr. Harwell Wilson's early recommendation to make the organization an inclusive society and welcome high-quality gastrointestinal surgeons regardless of allegiance to academia or private practice. Cross-fertilization has paid handsome benefits.

As I stated earlier, I cannot say that as a young surgeon I appreciated the potential value of the SSAT in the same way our founders did. I now recognize the importance of the Society's accomplishments in creating a surgical organization that has made us cognizant of the fact that gastrointestinal surgery is not something one can just "do"; rather it requires special education and training that we can provide without disruption of our current surgical training programs.

The Society for Surgery of the Alimentary Tract has a rich future. We need not be reticent about enunciating its accomplishments. I am particularly grateful for what the Society has done for me.

It is good to be reminded of the decisions of our predecessors that have brought us to our current level of achievement and leadership. It is the responsibility of all of us to guarantee the future. With regard to the future, one needs to refer to Dr. Pelligrini's Presidential Address and give serious consideration to his recommendations.

Again, I am pleased and proud to have been honored this morning. I thank you all so much.

Resected Adenocarcinoma of the Pancreas—616 Patients: Results, Outcomes, and Prognostic Indicators

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This large-volume, single-institution review examines factors influencing long-term survival after resection in patients with adenocarcinoma of the head, neck, uncinate process, body, or tail of the pancreas. Between January 1984 and July 1999 inclusive, 616 patients with adenocarcinoma of the pancreas underwent surgical resection. A retrospective analysis of a prospectively collected database was performed. Both univariate and multivariate models were used to determine the factors influencing survival. Of the 616 patients, 526 (85%) underwent pancreaticoduodenectomy for adenocarcinoma of the head, neck, or uncinate process of the pancreas, 52 (9%) underwent distal pancreatectomy for adenocarcinoma of the body or tail, and 38 (6%) underwent total pancreatectomy for adenocarcinoma extensively involving the gland. The mean age of the patients was 64.3 years, with 54% being male and 91% being white. The overall perioperative mortality rate was 2.3%, whereas the incidence of postoperative complications was 30%. The median postoperative length of stay was 11 days. The mean tumor diameter was 3.2 cm, with 72% of patients having positive lymph nodes, 30% having positive resection margins, and 36% having poorly differentiated tumors. Patients undergoing distal pancreatectomy for left-sided lesions had larger tumors (4.7 vs. 3.1 cm, $P < 0.0001$), but fewer node-positive resections (59% vs. 73%, $P = 0.03$) and fewer poorly differentiated tumors (29% vs. 36%, $P < 0.001$), as compared to those undergoing pancreaticoduodenectomy for right-sided lesions. The overall survival of the entire cohort was 63% at 1 year and 17% at 5 years, with a median survival of 17 months. For right-sided lesions the 1- and 5-year survival rates were 64% and 17%, respectively, compared to 50% and 15% for left-sided lesions. Factors shown to have favorable independent prognostic significance by multivariate analysis were negative resection margins (hazard ratio [HR] = 0.64, confidence interval [CI] = 0.50 to 0.82, $P = 0.0004$), tumor diameter less than 3 cm (HR = 0.72, CI = 0.57 to 0.90, $P = 0.004$), estimated blood loss less than 750 ml (HR = 0.75, CI = 0.58 to 0.96, $P = 0.02$), well/moderate tumor differentiation (HR = 0.71, CI = 0.56 to 0.90, $P = 0.005$), and postoperative chemoradiation (HR = 0.50, CI = 0.39 to 0.64, $P < 0.0001$). Tumor location in head, neck, or uncinate process approached significance in the final multivariate model (HR = 0.60, CI = 0.35 to 1.0, $P = 0.06$). Pancreatic resection remains the only hope for long-term survival in patients with adenocarcinoma of the pancreas. Completeness of resection and tumor characteristics including tumor size and degree of differentiation are important independent prognostic indicators. Adjuvant chemoradiation is a strong predictor of outcome and likely decreases the independent significance of tumor location and nodal status. (J GASTROINTEST SURG 2000;4:567-579.)

KEY WORDS: Pancreatic cancer, adenocarcinoma, prognostic factors, survival

Ductal adenocarcinoma is the most common primary malignancy of the pancreas. Approximately 65% of pancreatic adenocarcinomas arise in the head, neck, or uncinate process of the pancreas, 15% in the body or tail of the gland, and 20% diffusely involve the gland. Pancreatic adenocarcinoma remains the fifth leading cause of cancer deaths in the United States, with an overall 5-year survival rate of less than 4%.[1]

The minority of patients with adenocarcinoma of the pancreas have tumors amenable to surgical resec-

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tion. The resectability rate for body and tail lesions (left-sided) has been reported to be less than that for head, neck, and uncinate lesions (right-sided),[2] as patients with proximal lesions often develop obstructive jaundice and present earlier, while the disease is still localized to the pancreas and resectable. Those with distal lesions tend to have vague, nonspecific symptoms and often go undiagnosed until the disease is at an advanced stage.

Until the 1970s and early 1980s, the high morbidity and mortality rates following pancreatic resection led many surgeons to suggest that surgical resection of pancreatic cancers should be abandoned.[3,4] Over the past two decades, pancreatic resection has been performed with increasing frequency, with many specialized centers reporting acceptable morbidity rates and mortality rates of less than 5%.[2,5-9] Many factors are likely to be responsible for the improved safety of pancreatic resection, including improvements in critical care, increased surgical experience with decreased blood loss and operative time,[5,9] and regionalization to specialized centers of excellence.[10-12]

Many centers have also reported improved long-term survival following pancreatic resection, with 5-year actuarial survival rates of approximately 15% to 20% following pancreaticoduodenectomy[5-9] and approximately 10% following distal pancreatectomy.[2,13,14] A number of studies have analyzed the determinants of long-term survival in patients with resected pancreatic cancer. Factors associated with a favorable prognosis by univariate or multivariate models in the past have included age, extended retroperitoneal lymphadenectomy, negative resection margins, negative lymph node status, small tumor size, well/moderate tumor differentiation, diploid tumor DNA content, the absence of perioperative blood transfusions, low estimated intraoperative blood loss, tumor location, adjuvant chemoradiation, and molecular genetic findings.[5,6,15-25] These studies contained smaller numbers of patients with tumors in various locations and were inconsistent with regard to the factors influencing survival.

The current study represents the largest single-institution series of resected pancreatic cancers analyzed in the literature to date. The purpose of this report is to determine the factors influencing long-term survival after surgical resection. Demographic, intraoperative, pathologic, and postoperative factors were analyzed.

PATIENTS AND METHODS

Between January 1984 and July 1999 inclusive, 616 patients underwent surgical resection for adenocarcinoma of the pancreas at The Johns Hopkins Hospital. A retrospective review of a prospectively collected database was performed. Patients with neoplasms in the head, neck, or uncinate process of the gland underwent pancreaticoduodenectomy, whereas those with neoplasms in the body and tail underwent distal pancreatectomy. Total pancreatectomy was reserved for patients with tumors extensively involving the head of the pancreas but extending beyond the superior mesenteric vessels. The bias at this institution has been to perform pylorus-preserving resections, with distal gastrectomy reserved for tumors involving the distal stomach or proximal duodenum. Prior to 1996, no effort was made to perform a radical retroperitoneal lymph node dissection. However, as part of an ongoing randomized trial, retroperitoneal lymphadenectomy as well as distal gastrectomy were used more frequently after 1996.[26] All distal pancreatic resections included splenectomy and most extended proximally to the superior mesenteric vessels. In a small percentage of patients, pancreaticoduodenectomy was combined with resection of involved portal or superior mesenteric veins. Vagotomy, tube gastrostomy, and tube jejunostomy were not routinely performed, and total parenteral nutrition was not routinely used.

All pathology specimens were reviewed by an attending pathologist to determine the primary pathologic diagnosis and the extent of disease. To be included in the current study, the neoplasm had to have malignant histology with stromal, perineural, vascular, or lymphatic invasion. In addition, the tumor had to demonstrate epithelial and glandular differentiation by light microscopy. In poorly differentiated tumors, glandular differentiation was confirmed with mucicarmine staining. Only tumors showing primarily pancreatic ductal epithelial differentiation were included. For periampullary lesions, pancreatic ductal origin was determined using a histologic section taken through the distal bile duct at the level of the ampulla of Vater. Using previously defined criteria,[21] the tissue of origin was determined. Distal bile duct, ampullary, and duodenal adenocarcinomas were excluded. Mucinous and serous cystic neoplasms, solid and papillary neoplasms (Hamoudi tumors), intraductal papillary mucinous neoplasms, acinar cell carcinomas, and neuroendocrine tumors were also excluded.

The overall incidence of postoperative complications was evaluated. Delayed gastric emptying, pancreatic fistula, and biliary anastomotic leak were defined by previously reported criteria.[9,27,28] Standard definitions for wound infection, intra-abdominal abscess, pancreatitis, pneumonia, and cholangitis were used to evaluate the incidence of these postoperative complications.[9,17] Perioperative mortality was defined as death during the initial hospitalization or within 30 days of surgery.

During most of the study period, patients with pancreatic adenocarcinoma were evaluated by a mul-

tidisciplinary group (surgery, medical oncology, radiation oncology, and pathology) and postoperative chemoradiation therapy was encouraged. Standard chemoradiation therapy or new protocol therapies were performed at The Johns Hopkins Hospital or elsewhere. Patients also could choose not to undergo adjuvant therapy. The majority of patients receiving adjuvant therapy received standard chemoradiation protocols consisting of 4000 to 5000 cGy of external beam radiation to the tumor bed given with two 3-day courses of 5-fluorouracil (5-FU; 500 mg/m^2/day) followed by weekly bolus 5-FU for four additional months.[20,29,30] Other therapies included more intensive 5-FU plus leucovorin-based chemoradiation,[20,31,32] and chemoradiation including 5-FU, mitomycin C, leucovorin, and dipyridamole.[33]

Follow-up information was obtained through direct patient contact, review of hospital charts and surgeons' records, and by contacting the United States Social Security Administration. Complete survival information was available for 612 of the 616 patients. Many patients in the current study have been included in previous studies from this institution.*

Both univariate and multivariate methods were used to determine the prognostic significance of various factors in patients with pancreatic cancer. The factors analyzed included patient demographics, intraoperative factors (blood loss, blood transfusions, operative time, type and extent of resection), tumor characteristics (diameter, margin status, lymph node status, differentiation), and the use of postoperative chemoradiation. The primary outcome variable analyzed was survival.

All continuous data are presented as mean ± standard error of the mean. A chi-square test was used for all comparisons among categorical variables, whereas Student's *t* test was used for all comparisons among continuous variables. Survival analysis was performed using the method of Kaplan and Meier.[34] Univariate differences in survival among subgroups were compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazard model.[35] Significance was accepted at the 5% level.

RESULTS

Demographics and Intraoperative Factors (Table I)

In the 15 years of this study, 616 patients underwent potentially curative resection for adenocarcinoma of the pancreas. The mean age of the patients was 64.3 ± 0.4 years (median 66 years), with the youngest being 30 years and the oldest 89 years.

*References 8, 9, 16, 17, 20, 21, 26-28.

Table I. Demographics and intraoperative factors (n = 616)

	Number	Percent
Demographics		
Sex		
Male	335	54
Female	281	46
Age		
Mean ± SE	64.3 ± 0.4 yr	—
Median	66 yr	—
Race		
White	560	91
Black	36	6
Other	20	3
Intraoperative factors		
Type of operation		
Pancreaticoduodenectomy	526	85
Distal pancreatectomy	52	9
Total pancreatectomy	38	6
Estimated blood loss		
Mean ± SE	970 ± 40 ml	—
Median	750 ml	—
Transfusion requirements		
Mean ± SE	1.0 ± 0.9 units	—
Median	0 units	—
Operative time		
Mean ± SE	6.7 ± 0.1 hr	—
Median	6.5 hr	—
Vein resection	15	2

SE = standard error.

There were 335 men (54%) and 281 women (46%), with the racial distribution being 560 white (91%), 36 black (6%), and 20 other (3%).

Of the 616 patients, 526 (85%) underwent pancreaticoduodenectomy for adenocarcinoma in the head, neck, or uncinate process of the pancreas, 52 (9%) underwent distal pancreatectomy for adenocarcinoma of the body or tail, and 38 (6%) underwent total pancreatectomy, usually for adenocarcinoma involving the head and neck of the gland, but extending distally into the body of the pancreas.

The median intraoperative blood loss was 750 ml, with a median intraoperative blood transfusion requirement of zero units of packed red blood cells and a median operative time of 6.5 hours. Fifteen patients (2%) underwent resection of a portion of the superior mesenteric or portal vein with appropriate reconstruction.

For those patients undergoing pancreaticoduodenectomy or total pancreatectomy (n = 564), 396 (70%) were pylorus-preserving resections, whereas 30% were classic resections. Sixty-five patients underwent radical retroperitoneal lymphadenectomy

Table II. Tumor characteristics

	Overall (n = 616)	Pancreaticoduodenectomy/ total pancreatectomy (n = 564)	Distal pancreatectomy (n = 52)	*P* value
Tumor diameter				
Mean ± SE	3.2 ± 0.1 cm	3.1 ± 0.1 cm	4.7 ± 0.4 cm	<0.0001
Median	3.0 cm	3.0 cm	4.8 cm	
Resection margins				
Positive	30%	30%	20%	NS
Negative	70%	70%	80%	
Lymph node status				
Positive	73%	73%	59%	0.03
Negative	27%	27%	41%	
Differentiation				
Well	6%	4%	28%	<0.0001
Moderate	58%	60%	43%	
Poor	36%	36%	29%	

SE = standard error; NS = not significant.

as part of an ongoing prospective, randomized trial.[26] All patients undergoing radical lymphadenectomy also underwent classic resections including 30% to 40% distal gastrectomy. No patients undergoing distal pancreatectomy underwent a radical retroperitoneal lymph node dissection. Of the 526 partial pancreatectomies, pancreatic-enteric reconstruction was accomplished via pancreaticojejunostomy in 435 patients (83%) and pancreaticogastrostomy in 91 patients (17%).

Tumor Characteristics (Table II)

The mean tumor diameter for the entire cohort (n = 616) was 3.2 ± 0.1 cm, with a median tumor diameter of 3.0 cm. Six percent of the carcinomas were well differentiated, 58% were moderately differentiated, and 36% were poorly differentiated. Thirty percent of patients had positive resection margins on final pathology, whereas 73% of patients had tumor involvement of lymph nodes within the resection specimen. The most common site of positive resection margins was the uncinate process margin along the superior mesenteric artery. Of the 65 patients undergoing pancreaticoduodenectomy with radical retroperitoneal lymphadenectomy, 15 (23%) had involvement of the retroperitoneal lymph nodes with metastatic tumor. There was no instance of retroperitoneal nodal involvement in the absence of positive pancreaticoduodenal specimen nodes.

Patients with lesions in the head, neck, or uncinate process of the pancreas had significantly smaller tumors (3.1 ± 0.1 cm) as compared to those patients with lesions in the body or tail of the gland (4.7 ± 0.4 cm, $P < 0.0001$). Thirty percent of right-sided tumors were resected with positive margins, compared to 20% of left-sided lesions (P = NS). Despite the smaller tumor diameter observed in right-sided tumors, there was a significantly higher incidence of nodal positivity for right-sided tumors (73% vs. 59%, $P = 0.03$). Additionally, right-sided tumors were histologically less differentiated. Only 4% of patients with right-sided tumors had well-differentiated tumors, whereas 28% of patients with left-sided tumors had well-differentiated tumors ($P < 0.0001$).

Postoperative Course (Table III)

There were 14 deaths in the series for an overall perioperative mortality rate of 2.3%. Five of the 14 deaths were from intra-abdominal or gastrointestinal hemorrhage and five were from intra-abdominal sepsis. Two patients died of ischemic bowel and one died of hepatic necrosis with fulminant hepatic failure. The final patient suffered a portal/superior mesenteric venous injury intraoperatively and died on postoperative day 3 of ischemic bowel and multisystem organ failure. The mortality rate was 2.3% for pancreaticoduodenectomy and 1.9% for distal pancreatectomy (P = NS).

The overall complication rate was 30% for the entire cohort, with 31% of patients undergoing pancreaticoduodenectomy and 25% of patients undergoing distal pancreatectomy experiencing postoperative complications (P = NS). Three percent of patients undergoing pancreaticoduodenectomy and 4% of patients undergoing distal pancreatectomy required reoperation during the immediate postoperative period,

Table III. Postoperative course

	Overall (n = 616)	Pancreaticoduodenectomy/ total pancreatectomy (n = 564)	Distal pancreatectomy (n = 52)	*P* value
Perioperative mortality	2.3%	2.3%	1.9%	NS
Overall complications	30%	31%	25%	NS
Specific complications				
Reoperation	3%	3%	4%	NS
Delayed gastric emptying	—	14%	—	—
Cholangitis	—	3%	—	—
Bile leak	—	2%	—	—
Wound infection	7%	7%	5%	NS
Pancreatic fistula	5%	5%	8%	NS
Intra-abdominal abscess	3%	3%	4%	NS
Pneumonia	1%	1%	0%	NS
Pancreatitis	1%	1%	0%	NS
Postoperative length of stay				
Mean ± SE	13.7 ± 0.4 days	14.0 ± 0.4 days	11.5 ± 2.2 days	0.08
Median	11 days	11 days	7 days	

most commonly for bleeding or intra-abdominal sepsis. Delayed gastric emptying, cholangitis, and bile leaks were seen only in those patients undergoing pancreaticoduodenectomy or total pancreatectomy (n = 564), with incidences of 14%, 3%, and 2%, respectively. Delayed gastric emptying was the most commonly observed complication. In order of decreasing frequency, wound infection was observed in 7% of the entire cohort, pancreatic fistula in 5%, intra-abdominal abscess in 3%, pneumonia in 1%, and pancreatitis in 1%. There were no significant differences in the frequencies of these specific complications when the pancreaticoduodenectomy and the distal pancreatectomy groups were compared.

The mean postoperative length of stay was 13.7 ± 0.4 days (median 11 days) for the entire cohort of 616 patients. For those undergoing pancreaticoduodenectomy, the mean postoperative length of stay was 14.0 ± 0.4 days (median 11 days) compared to 11.5 ± 2.2 days (median 7 days) for those undergoing distal pancreatectomy ($P = 0.08$).

Adjuvant Therapy

Information regarding postoperative combined-modality therapy was available for 498 (81%) of the 616 patients. Much of the missing chemoradiation data were from patients undergoing surgery within the last year, many of whom had not decided on or had not completed a postoperative treatment plan prior to data analysis. Of the 498 patients from whom adjuvant therapy data were available, 366 patients (74%) received adjuvant chemoradiation and 132 (26%) declined adjuvant therapy for various reasons. The vast majority of those undergoing chemoradiation received standard 5-FU–based therapy.

Factors Influencing Survival—Univariate Analysis (Table IV)

The mean live patient follow-up was 24.1 ± 1.9 months, with a median follow-up of 13 months. At the time of analysis, 201 of the 612 patients were alive. The overall Kaplan-Meier actuarial survival was 63% at 1 year, 25% at 3 years, and 17% at 5 years, with a median survival of 17 months (Fig. 1). Two hundred eight patients were operated on 5 or more years ago, with 33 five-year survivors, yielding an actual 5-year survival of 17%. Of the 33 five-year survivors, there were nine 7-year survivors and two 10-year survivors.

When examining demographic factors, survival was similar among patients under 65 years of age and those 65 years or older, in males and females, and in whites and nonwhites. The decade of resection (1980s vs. 1990s) also had no impact on long-term survival. The effect of intraoperative factors on survival was also examined. In a univariate analysis, the location of the tumor approached significance. Patients with right-sided tumors requiring pancreaticoduodenectomy or total pancreatectomy had 1- and 5-year survival rates of 64% and 17%, respectively (median = 18 months), whereas those with body or tail lesions requiring distal pancreatectomy had 1- and 5-year survival rates of 50% and 15% (median = 12 months; $P = 0.06$, Fig. 2). Patients with an estimated intraoperative blood loss of less than 750 ml had significantly better long-term survival than those with an

Table IV. Factors influencing survival—univariate analysis

Factor	No. of patients	1-Year (%)	5-Year (%)	Median (mo)	*P* value
Overall	612	63	17	17	—
All patients					
Head, neck, or uncinate	563	64	17	18	0.06
Body or tail	49	50	15	12	
Estimated blood loss <750 ml	294	71	20	20	0.003
Estimated blood loss ≥750 ml	295	55	14	14	
No transfusions	372	69	18	19	0.04
Transfusions	217	54	16	14	
Negative margins	423	69	21	19	<0.0001
Positive margins	184	49	6	12	
Negative nodes	166	68	22	20	0.006
Positive nodes	441	61	14	16	
Diameter <3 cm	268	72	22	21	<0.0001
Diameter ≥3 cm	325	56	12	14	
Well/moderate differentiation	380	67	18	19	0.0003
Poor differentiation	216	56	13	14	
Adjuvant therapy	333	71	20	19	<0.0001
No adjuvant therapy	119	48	9	11	
Head, neck, or uncinate lesions only					
Plyorus-preserving	395	64	16	17	NS
Classic	168	66	20	19	
Partial pancreatectomy	526	65	18	18	0.05
Total pancreatectomy	37	50	4	11	

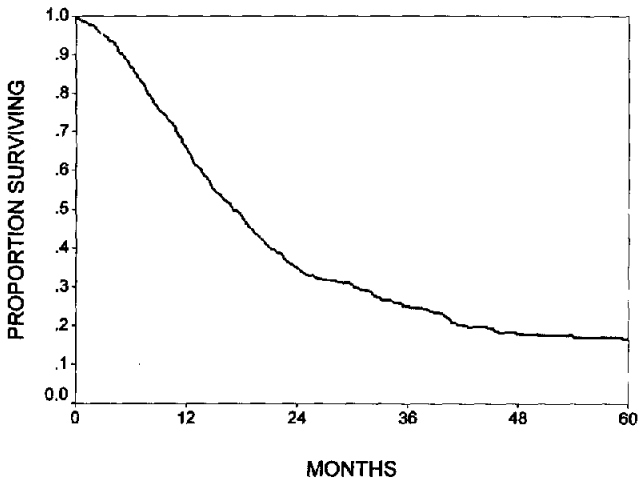

Fig. 1. Kaplan-Meier actuarial survival for entire cohort of 616 patients with resected pancreatic adenocarcinoma.

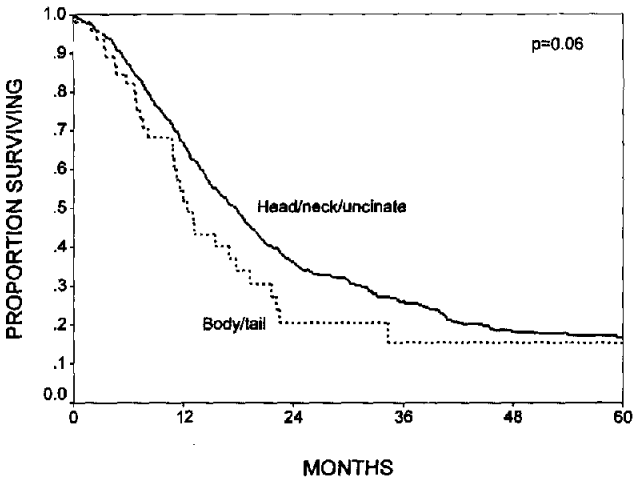

Fig. 2. Kaplan-Meier actuarial survival curves comparing patients with head, neck, and uncinate lesions (right-sided, n = 563) to those with body and tail lesions (left-sided, n = 49).

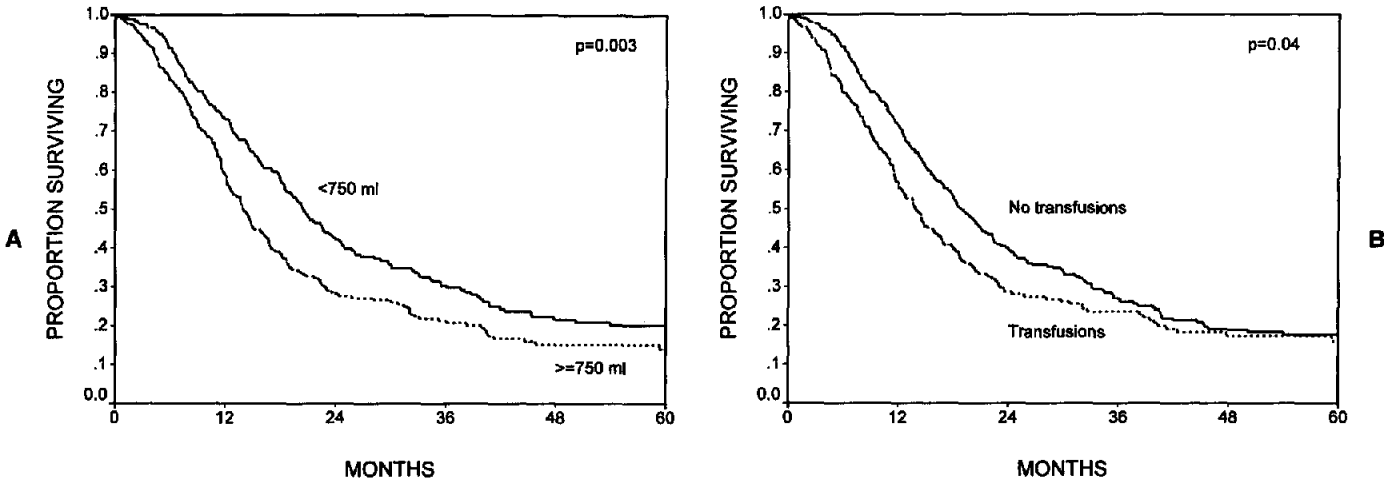

Fig. 3. A, Kaplan-Meier actuarial survival curves comparing patients with estimated intraoperative blood loss <750 ml (n = 294) to those with estimated intraoperative blood loss ≥750 ml (n = 295). B, Kaplan-Meier actuarial survival curves comparing patients requiring no intraoperative blood transfusions (n = 372) to those receiving blood transfusions (n = 217).

estimated blood loss of 750 ml or more, with 1- and 5-year survival rates of 71% and 20% (median = 20 months) compared to 55% and 14%, respectively (median = 14 months; $P = 0.003$, Fig. 3, *A*). Similarly, those patients not requiring intraoperative blood transfusions fared significantly better, with 1- and 5-year survival rates of 69% and 18% (median = 19 months) compared to 54% and 16% for those receiving transfusions (median = 14 months; $P = 0.04$, Fig. 3, *B*). Operative time did not influence survival.

Several tumor characteristics proved to be important prognostic indicators. Patients with negative resection margins had 1- and 5-year survival rates of 69% and 21% (median = 19 months), whereas those with positive resection margins had 1- and 5-year survival rates of 49% and 6% (median = 12 months; $P < 0.0001$, Fig. 4, *A*). Those with negative lymph nodes had better long-term survival than those with lymph node metastases, with 1- and 5-year survival rates of 68% and 22% (median = 20 months) vs. 61% and 14% (median = 16 months; $P = 0.006$, Fig. 4, *B*). Patients with smaller tumors fared better, with 1- and 5-year survival rates of 72% and 22% (median = 21 months) for tumors smaller than 3 cm compared to 56% and 12% (median = 14 months) for tumors 3 cm or larger (Fig. 4, *C*; $P < 0.0001$). Seventy-five patients (12%) had tumors smaller than 3 cm and underwent margin-negative, node-negative resections. This select group of patients had 1-, 3-, and 5-year survival rates of 81%, 46%, and 31%, respectively (median = 33 months). Tumor differentiation was also a significant prognostic factor with 1- and 5-year survival rates of 67% and 18% (median = 19 months) for (well/moderately differentiated tumors and 56% and 13% median = 14 months) for poorly differentiated tumors ($P = 0.0003$; Fig. 4, *D*).

Combined-modality adjuvant therapy also favorably influenced survival. Those patients receiving adjuvant chemoradiation had 1- and 5-year survival rates of 71% and 20% (median = 19 months) compared to 48% and 9% (median = 11 months) for those not receiving therapy ($P < 0.0001$; Fig. 5).

For those patients undergoing pancreaticoduodenectomy or total pancreatectomy, the type of resection (pylorus-preserving vs. classic) had no impact on survival. Those patients undergoing partial pancreatectomy had better long-term survival than those undergoing total pancreatectomy, with 1- and 5-year survival rates of 65% and 18% (median = 18 months) vs. 50% and 4%, respectively (median = 11 months; $P = 0.05$). For the 498 patients undergoing standard pancreaticoduodenectomy, the 1- and 5-year survival rates were 63% and 16% (median = 17 months) compared to 81% at 1 year (median = 29 months) for those undergoing pancreaticoduodenectomy plus radical retroperitoneal lymphadenectomy ($P = 0.01$). However, this comparison is invalid since the patients undergoing retroperitoneal lymphadenectomy are part of a prospective, randomized trial that began only in April 1996. Considering only those patients randomized between standard resection (n = 64) and radical resection (n = 65), the 1-, 2-, and 3-year survival rates are 71%, 40%, and 32% for the standard resection group (median = 20 months) compared to

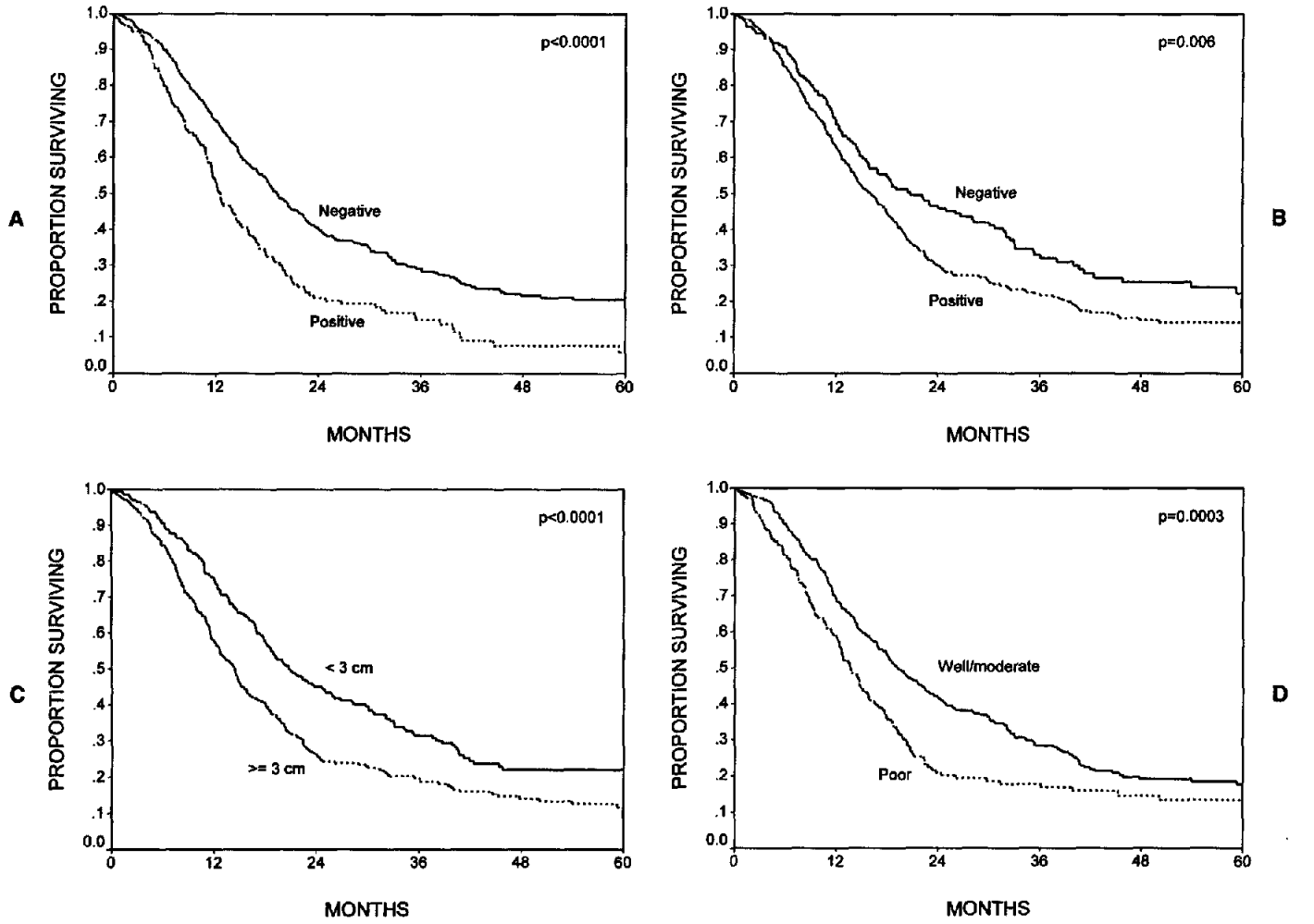

Fig. 4. **A**, Kaplan-Meier actuarial survival curves comparing patients with negative resection margins (n = 423) to those with positive resection margins (n = 184). **B**, Kaplan-Meier actuarial survival curves comparing patients with negative lymph nodes (n = 166) to those with positive lymph nodes (n = 441). **C**, Kaplan-Meier actuarial survival curves comparing patients with tumor diameter <3 cm (n = 268) to those with tumor diameter ≥3 cm (n = 325). **D**, Kaplan-Meier actuarial survival curves comparing patients with well/moderate tumor differentiation (n = 380) to those with poor tumor differentiation (n = 216).

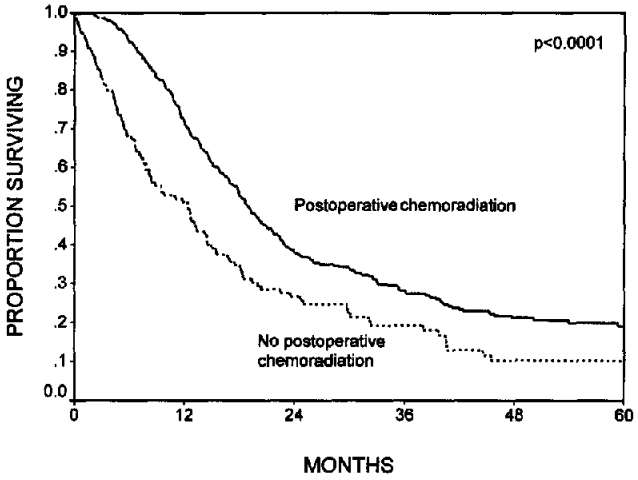

Fig. 5. Kaplan-Meier actuarial survival curves comparing patients receiving postoperative chemoradiation (n = 333) to those not receiving postoperative chemoradiation (n = 119).

Table V. Factors influencing survival—multivariate analysis

Factor	Hazard ratio	Confidence interval	*P* value
Overall cohort			
Negative resection margins	0.64	0.50-0.82	0.0004
Tumor diameter <3 cm	0.72	0.57-0.90	0.004
Well/moderate differentiation	0.71	0.56-0.90	0.005
Estimated blood loss <750 ml	0.75	0.58-0.96	0.02
Adjuvant chemoradiation	0.50	0.39-0.64	<0.0001
Tumor in head, neck, or uncinate	0.60	0.35-1.00	0.06
Negative lymph nodes	0.88	0.68-1.13	0.32
No blood transfusions	0.96	0.75-1.23	0.76
Head, neck, or uncinate lesions only			
Negative resection margins	0.64	0.49-0.82	0.0005
Tumor diameter <3 cm	0.73	0.58-0.93	0.01
Well/moderate differentiation	0.72	0.57-0.92	0.008
Estimated blood loss <750 ml	0.76	0.59-0.98	0.04
Adjuvant chemoradiation	0.49	0.38-0.63	<0.0001
Tumor in head, neck, or uncinate	0.81	0.51-1.30	0.39
Negative lymph nodes	0.88	0.67-1.14	0.33
No blood transfusions	0.98	0.76-1.27	0.90
Classic pancreaticoduodenectomy	0.96	0.77-1.97	0.78

81%, 57%, and 41% for radical resection group (median = 32 months; $P = 0.3$). These differences are not statistically significant, but the clinical trial is ongoing.

Survival—Multivariate Analysis (Table V)

A multivariate survival analysis was performed on the entire cohort to determine which univariate prognostic relationships were independent predictors of improved survival and which were the result of confounding. In the final model, 448 patients were available for analysis, with 325 deaths. Patients were excluded from the multivariate model if information regarding any factors analyzed was not available. The most common reason was lack of chemoradiation data in more recent patients. Demographic factors included in the final multivariate model had no prognostic significance. Factors shown to have favorable independent prognostic significance by this multivariate analysis were negative resection margins (hazard ratio [HR] = 0.64, confidence interval [CI] = 0.50 to 0.82, $P = 0.0004$), tumor diameter less than 3 cm (HR = 0.72, CI = 0.57 to 0.90, $P = 0.004$), well/moderate tumor differentiation (HR = 0.71, CI = 0.56 to 0.90, $P = 0.005$), estimated blood loss less than 750 ml (HR = 0.75, CI = 0.58 to 0.96, $P = 0.02$), and adjuvant chemoradiation (HR = 0.50, CI = 0.39 to 0.64, $P < 0.0001$). Tumor location in the head, neck, or uncinate process approached significance in this final multivariate model (HR = 0.60, CI = 0.35 to 1.0, $P = 0.06$). Negative nodal status and no blood transfusions were significant in the univariate model but were not significant in the final multivariate model ($P = 0.32$ and $P = 0.76$, respectively).

A similar multivariate model was developed for lesions in the head, neck, and uncinate process. The final model included 426 patients, with 310 deaths. Location was compared as in the above-mentioned model, but in this case head, neck, and uncinate lesions were compared to diffuse lesions. In addition to the factors used in the previous model, the type of resection (pylorus-preserving vs. classic) was included in the final model. All factors that were significant in the previous model remained significant. Location (head, neck, or uncinate vs. diffuse) and type of resection did not have independent prognostic significance.

DISCUSSION

In the past two decades, pancreatic resection for adenocarcinoma of the pancreas has been associated with decreasing morbidity and mortality as well as improved long-term survival.[2,5-9,21] The current report represents the largest single-institution series of resected pancreatic adenocarcinomas in the literature to date. It includes carcinomas involving the proximal portion of the gland (head, neck, or uncinate), carcinomas involving the distal portion of the gland (body or tail), and those extensively involving the gland. Consistent with previous reports,[5-9,20,21] the results of

this current single-institution experience demonstrate an overall actuarial 5-year survival rate of 17% following resection. Further, the actual 5-year survival was 17% for the cohort of 208 patients followed for at least 5 years. By univariate analysis, the actuarial 5-year survival was improved in patients with an estimated intraoperative blood loss of less than 750 ml, no blood transfusions, negative resection margins, negative lymph nodes, tumors less than 3 cm, and well/moderately differentiated tumors and in those receiving adjuvant chemoradiation. Using a multivariate analysis, the factors shown to have favorable independent prognostic significance were negative resection margins, tumor diameter less than 3 cm, well/moderate tumor differentiation, estimated blood loss less than 750 ml, and adjuvant chemoradiation.

There is an obvious relationship between estimated blood loss and intraoperative transfusion requirements. In previous analyses, intraoperative blood loss[17] and/or transfusion requirements[5,17,20] were found to be predictors of long-term survival. Both were significant in the current univariate analysis, but only estimated blood loss remained significant in the multivariate model. It is unclear if estimated blood loss itself is an important prognostic variable, or if it somehow serves as a surrogate for other factors such as preoperative anemia, debilitation, cachexia, or some other factor. Certainly it is our practice to minimize intraoperative blood loss via careful surgical technique and hemostasis. Further, we do not routinely transfuse patients at some arbitrary hemoglobin value, unless there is underlying ischemic cardiac disease.[36]

Patients with lesions in the head, neck, or uncinate process demonstrated improved 1-year (64% vs. 50%) and median survival (18 vs. 12 months), but similar 5-year survival (17% vs. 15%), when compared to those with tumors in the body or tail, but this did not quite achieve statistical significance ($P = 0.06$). The same trend is observed in the multivariate model. When compared to patients with right-sided lesions, those with left-sided pancreatic cancers are more often unresectable at the time of presentation and thus were not included in our analysis. Right-sided lesions tend to present earlier because of their proximity to the distal common bile duct and the resultant obstructive jaundice. Distal lesions usually present later, likely as a result of vague symptomatology and subsequent delay in diagnosis. As seen in this series, patients with resected right- and left-sided tumors had similar percentages of positive resection margins (30% vs. 20%, respectively; P = NS). Left-sided tumors were significantly larger than right-sided tumors (4.8 vs. 3.0 cm; $P < 0.0001$), supporting the concept of a later diagnosis. Those left-sided tumors that are resectable likely represent a select group of biologically more indolent tumors, as demonstrated by the lower incidence of nodal positivity (59% vs. 73%; $P = 0.03$). The smaller percentage of left-sided tumors in the series and the lower resectability rate for these tumors likely accounts for the lack of significance in the postresection survival models.

As would be expected, completeness of resection and tumor characteristics were important in predicting long-term survival. Since pancreaticoduodenectomy offers the only chance for long-term survival in patients with pancreatic adenocarcinoma, we often resect large tumors, leaving microscopic tumor at the surgical margins in 30% of all cases. Intraoperative frozen sections of the pancreatic neck and common hepatic duct margins are routinely performed, and further resection at these sites is performed when indicated. Therefore the most common site of final positive resection margins is the uncinate process along the superior mesenteric artery. Although the surgeon can usually assess the relationship of the tumor to the superior mesenteric and portal veins relatively early in the course of resection, the relationship of the tumor to the superior mesenteric artery often cannot be determined until after the bile duct and pancreatic neck have been transected. Frozen sections of the uncinate process margin are performed; however, further resection to achieve negative margins is usually not possible as it is our practice to dissect the uncinate process off flush with the superior mesenteric artery and vein. Often these vessels are infiltrated with tumor and negative margins cannot be achieved without major vascular resection. Patients with negative resection margins, negative nodal status, tumor diameters less than 3 cm, and well or moderately differentiated tumors fared better by univariate analysis, all of which have been demonstrated in previous series. In the multivariate model, all the preceding factors with the exception of nodal status remained significant. Quite importantly, the highly favorable subgroup of patients (12% of the group) with tumors less than 3 cm in diameter, negative lymph nodes, and negative resection margins have a 5-year actuarial survival rate of 31%, suggesting a true benefit for early detection. Recognition of high-risk populations and the development of reliable tumor markers for more effective screening and earlier detection will likely contribute to improved survival in the future.

Nodal status has been evaluated in multiple series, with many finding significant impact on long-term survival in univariate or multivariate models.[2,6,9,17,21] In our previous report of 201 patients with adenocarcinoma of the head of the pancreas,[16] nodal status was a significant predictor of survival in both the univari-

ate and multivariate models. However, in that series, adjuvant therapy data were not available for the majority of patients and adjuvant therapy was not included in the final multivariate analysis. The independent significance of lymph node metastases may be decreased by the increased utilization of postoperative chemoradiation therapy.

Adjuvant chemoradiation has been used increasingly since the early 1980s. The majority of patients in the current series elected to receive postoperative combined-modality therapy. The most often quoted reports on the use of adjuvant chemoradiation come from the Gastrointestinal Tumor Study Group in 1985 and 1987 and demonstrated improved survival with 5-FU–based chemotherapy plus external beam radiation to the pancreatic bed.[29,30] As described in a prior report from The Johns Hopkins Hospital,[20] patients with pancreatic adenocarcinoma were offered three options following resection: (1) standard therapy with radiation to the tumor bed and intermittent bolus 5-FU therapy; (2) intensive therapy, with radiation to the tumor bed as well as prophylactic hepatic irradiation and continuous-infusion 5-FU; and (3) no adjuvant therapy. By univariate analysis, patients who received either type of adjuvant therapy had a median survival of 19.5 months and a 2-year survival rate of 39%, which was significantly improved compared to those receiving no therapy (13.5 months and 30%, $P = 0.003$). By multivariate analysis, both adjuvant protocols had a significant positive impact on survival. The more intensive regimen did not appear to improve survival over standard therapy. In this current much larger series, the use of adjuvant therapy appears to be a significant predictor of long-term survival by both univariate and multivariate analysis, likely contributing to the decreased significance of nodal status and tumor location in the final multivariate model. Despite these data supporting the use of postoperative chemoradiation, there are some data that do not support its use.[37,38] Further well-conceived trials and the development of rational drug therapies are necessary to better define the appropriate use of chemoradiation therapy in resectable pancreatic adenocarcinoma.

A multivariate analysis of the subgroup of patients with right-sided tumors was performed because several controversies remain surrounding the technique of pancreaticoduodenectomy. These include classic versus pylorus-preserving pancreaticoduodenectomy and the extent of pancreatic resection (partial vs. total pancreatectomy). Some groups have advocated against pylorus preservation because of concern that microscopic tumor will be left in the proximal duodenum[39] and the fact that it does not allow lymph node dissection in the peripyloric and perigastric regions.[40] Despite these concerns, several studies have shown no decrease in survival and improved gastrointestinal outcomes when comparing pylorus-preserving and standard procedures.[5,17,41-43] Pylorus preservation shortens the operative time, retains the entire stomach as a reservoir, and maintains a more normal gastrointestinal milieu.[44,45] The current series suggests that the use of pylorus preservation in the treatment of proximal pancreatic cancers does not negatively influence survival.

In the current study, total pancreatectomy was used only in cases where tumor extended distally into the body of the pancreas. Therefore it is not surprising that long-term survival was decreased in the univariate model in the minority of patients requiring total pancreatectomy. Total pancreatectomy was not, however, significant in the multivariate model. Its use would not be likely to improve survival in patients with tumors adequately resected with partial pancreatectomy. Further, there would appear to be no advantage to total pancreatic resection, with its obligate need for pancreatic enzyme supplementation and insulin administration.

In summary, this large-volume, single-institution analysis of 616 patients allows for re-evaluation of demographic, intraoperative, pathologic, and postoperative factors and their effect on survival. Tumor characteristics such as negative resection margins, tumor size less than 3 cm, and well/moderate tumor differentiation are independent favorable prognostic indicators of long-term survival. Estimated blood loss was the only intraoperative parameter shown to have independent prognostic significance. Adjuvant chemoradiation is a strong predictor of outcome and likely decreases the independent significance of nodal status and tumor location. Although patients with body and tail lesions may present later, those with resectable tumors have long-term survival similar to that seen for patients with cancers in the head, neck, or uncinate process.

For patients with pancreatic adenocarcinoma, there is a pressing need for advances in our early detection abilities and therapeutic interventions. At this time, pancreatic resection remains the only hope for long-term survival. Further advances in adjuvant therapy, including immunotherapy, new chemotherapeutic agents, rational drug therapy, and novel combinations of chemotherapy and radiation, will likely contribute to future improvements in survival. Developments in the field of molecular genetics may allow for earlier detection through gene-based detection of common mutations in readily available clinical specimens such as stool,[46] blood, pancreatic juice,[47] and duodenal juice.[48]

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Effective Treatment of Pancreatic Tumors With Two Multimutated Herpes Simplex Oncolytic Viruses

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Pancreatic cancer is an aggressive, rapidly fatal disease against which current nonsurgical therapy has minimal impact. This study evaluates the efficacy of two novel, replication-competent, multimutated herpes viruses (G207 and NV1020) in an experimental model of pancreatic cancer. Four human pancreatic carcinoma cell lines were exposed to G207 or NV1020, and cell survival and viral progeny production were determined. Flank tumors in athymic mice were subjected to single or multiple injections of 1×10^7 G207 or NV1020, and tumor volume was evaluated over time. For all of the cell lines, G207 and NV1020 produced infection, viral replication, and cell lysis ($P < 0.05$). NV1020 resulted in a higher production of viral progeny compared to G207. The efficacy of viral tumor cell kill was greatest in those cells with the shortest in vitro doubling time. For flank tumors derived from hs766t, single or multiple injections of both viruses were equally effective and significantly reduced flank tumor burden ($P < 0.05$). Complete hs766t flank tumor eradication was achieved in 25% (5 of 20) of animals treated with G207 and 40% (8 of 20) of animals treated with NV1020. In vivo efficacy correlated with in vivo tumor doubling time. There were no adverse effects related to viral administration observed in any animal. NV1020 and G207 effectively infect and kill human pancreatic cancer cells in vitro and in vivo. Given the lack of effective nonoperative treatments for pancreatic cancer, oncolytic herpes viruses should be considered for clinical evaluation. (J GASTROINTEST SURG 2000;4:580-588.)

KEY WORDS: G207, NV1020, pancreatic carcinoma, R7020, herpes simplex virus, HSV-1, HSV-2, gene therapy

Pancreatic cancer is an aggressive malignancy with 5-year survival rates of 1% to 4%.[1] It is estimated that there will be 28,300 new cases and 28,200 deaths from pancreatic cancer in 2000.[2] Resection is the only treatment that offers the possibility of long-term survival. Recurrence is common, however, even after complete resection. Currently available therapies have been disappointing in their ability to reduce the incidence of recurrence and have a very limited impact in patients with unresectable disease. Novel treatment strategies are therefore necessary to further reduce the morbidity and mortality of pancreatic cancer.

The use of viruses is central to many antineoplastic strategies that have proved effective in experimental models. Many of these approaches use replication-defective viruses as vectors to transfer genes encoding protein products, such as immunostimulating cytokines,[3,4] prodrugs,[5,6] tumor suppressor genes,[7,8] or other agents. An alternative approach uses replication-competent viruses to infect and lyse tumor cells. In this regard, a number of viruses are currently being examined as treatment for cancer, such as Newcastle disease virus,[9] adenovirus,[10] and herpes simplex viruses.[11-14] A major advantage of replication-competent oncolytic viruses is that they may be administered in relatively small doses because the lytic life cycle generates progeny viruses capable of lysing additional target cells.

Oncolytic herpes viruses were originally examined for the treatment of neurologic tumors, attempting to exploit the natural neurotropism of herpes simplex virus (HSV)[15] and using strains genetically engineered

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to have reduced cytotoxicity to normal tissues and increased specificity toward tumor cells.[15] Initial success spawned further research into the use of these viruses in non-neurologic tumors. Replication-competent oncolytic herpes simplex viruses were subsequently shown to infect and kill diverse cancer types.[11,14,16-19] Two promising viruses in the current generation of replication-competent herpes simplex viruses are G207 and NV1020 (also known as R7020). Both were developed from the strain F backbone of HSV type 1. G207 is a virus designed specifically for cancer therapy that has had both copies of the natural $\gamma_1 34.5$ gene deleted to decrease HSV neurovirulence and the ICP6 gene inactivated to increase the specificity of G207 for rapidly dividing cells.[20,21] NV1020 was initially designed as a vaccine against HSV type 1 and 2 infections and has one copy of the $\gamma_1 34.5$ gene deleted, as well as other gene rearrangements to decrease virulence.[22] The ICP6 gene is intact. This report describes the use of these viruses in the treatment of experimental pancreatic cancer. The data show that both viruses have significant activity against human pancreatic cancer cell lines, both in vitro and in vivo, and that efficacy is greatest in more rapidly dividing cells.

MATERIAL AND METHODS

Viruses

G207 was constructed as previously described.[20] Both copies of the $\gamma_1 34.5$ gene were deleted and the *E. coli* lacZ gene was inserted into the U_L39 sequence to disable production of ribonucleotide reductase.[20] NV1020 was clonally derived from R7020 and constructed as previously described.[22] NV1020 has a 15 kb deletion over the joint region of the HSV-1 genome, which encompasses the genes ICP0, ICP4, and one copy of $\gamma_1 34.5$, as well as latency-associated transcripts. It also has a 700 bp deletion of the endogenous thymidine kinase (TK) locus that prevents expression of the overlapping transcripts of the U_L24 gene. In addition, a 5229 bp fragment of HSV-2 DNA encoding for several glycoprotein genes was inserted into the deleted joint region. An exogenous copy of the HSV-2 TK genes was also inserted, under the control of the $\alpha 4$ promoter. Virus at a multiplicity of infection (MOI) of 0.02 was propagated in African green monkey kidney (VERO) cells obtained from American Type Culture Collection (ATCC, Rockville, Md.) and maintained in Dulbecco's modified Eagle medium and 5% fetal bovine serum. Two days after infection, VERO cells were subjected to freeze-thaw lysis and sonication to release virus. Cell lysates were clarified by centrifugation (300 × *g* for 10 minutes at 4° C), and supernatant fractions containing virus were stored at −80° C. Viral titers were confirmed by plaque assays. Virus was stored at −80° C in NaCl–20 mmol/L Tris at pH 7.5.

Cell Culture

Four human pancreatic cancer cell lines purchased from ATCC were maintained at 37° C in a 5% carbon dioxide humidified atmosphere. HTB147, hs766t (HTB134), and PANC-1 (CRL1469) were maintained in Dulbecco's modified Eagle medium with 4.5 g/L glucose and 10% fetal bovine serum. AsPC (CRL1682) was maintained in RPMI 1640 with sodium pyruvate and 10% fetal bovine serum.

Population Doubling Time

Cells were plated at 5×10^4 cells in replicate T-25 flasks (Costar Corp., Cambridge, Mass.). Over the following 7 days, at 12-hour intervals, monolayers were trypsinized and cells counted on a hemacytometer using trypan blue exclusion. The average number of cells at each time point ($n = 2$) was plotted as a function of time, and doubling time was extrapolated.

Survival Assay

Viability of the four human pancreatic cancer cell line populations after exposure to G207 or NV1020 was determined as follows: cells were plated at a density of 4×10^4 cells per well in 24-well plates (Costar Corp.). Twelve hours later, medium was aspirated and the appropriate concentration of virus in fresh medium was applied in a final volume of 1 ml. Virus was added at multiplicities of infection (ratio of virus to cells) of 0.01, 0.1, and 1.0. At 1, 2, 3, and 4 days after infection, wells were washed with 0.25% EDTA and exposed to 0.25% trypsin. Cells were counted on a hemacytometer using trypan blue exclusion of nonviable cells. Assays were performed in triplicate. Survival of each cell line population was calculated as the number of cells in treatment groups divided by the number of cells in control (medium only) wells and multiplied by 100%.

Viral Plaque Assays

To demonstrate viral replication, standard plaque assays were performed in duplicate on hs766t and HTB147 cell lysates and supernates. The cell lines chosen for plaque assay had the longest and shortest doubling times, respectively. Cells plated at 5×10^5 cells per well in six-well plates (Costar Corp.) were infected with G207 or NV1020 at MOI 0.01. For each daily time point, cells were scraped from each

well in their medium, transferred to 15 ml polypropylene tubes (Becton Dickinson Labware, Franklin Lakes, N.J.), and subjected to four cycles of freeze-thaw lysis, and centrifugation at 3000 × *g* for 10 minutes at 4° C. Supernatant fractions were added to confluent VERO cells for standard plaque assay. Plaques were counted 3 days after VERO cell infection, and recovered titers were determined. MOI was calculated by dividing recovered titers by the number of viable cells in the survival assay.

Treatment of Flank Tumors in Athymic Mice

All experiments were performed with approval of the Memorial Sloan-Kettering Institutional Animal Care and Use Committee. Animals were housed in pathogen-free quarters in the animal facility, and weighed and examined three times per week.

Separate experiments with hs766t and HTB147 human pancreatic cancer cells were performed identically. The cell lines chosen for the in vivo study had the longest and shortest doubling times, respectively. Twenty-five athymic mice (National Cancer Institute), aged 4 to 6 weeks, were anesthetized with methoxyflurane inhalation; 2×10^6 cells of the pancreatic cancer cell line were injected subcutaneously in serum-free medium bilaterally on the flank. Tumors were measured three times per week. Tumor volume was calculated using the formula $4/3\pi ab^2$, where "a" is the radius of the long axis and "b" the radius of the short axis in millimeters. When tumor volume reached 22 ± 3 and 30 ± 3 mm^3 (± SEM) for hs766t and HTB147, respectively, animals were sorted into five treatment groups of n = 10 tumors for injection of agents in a volume of 0.075 ml serum-free medium as follows: single dose of 1×10^7 plaque-forming units (pfu) G207, three daily doses of 1×10^7 pfu G207, single dose of 1×10^7 pfu NV1020, three daily doses of 1×10^7 pfu NV1020, or three daily doses of serum-free medium. Duration of response was monitored for 3 weeks. Control medium, both in vitro and in vivo, was either serum-free medium or phosphate-buffered saline solution. Previous studies in our laboratory showed no difference between the heat-inactivated virus and culture media or phosphate-buffered saline solution alone.

Statistical Analysis

Student's two-tailed *t* test was used to determine significance between various treatment groups in both the in vitro and in vivo experiments.

RESULTS

Survival Assay

Survival of the cell lines after infection with G207 or NV1020 decreased compared to control specimens after 1 day of treatment (Student's *t* test, $P < 0.05$) for all MOIs tested (Fig. 1). A virus-to-cell ratio (MOI) of 1 was more effective in killing cells than MOIs 0.1 and 0.01 for all cell lines ($P < 0.05$). At 4 days, HTB147 and AsPC infected with G207 or NV1020 at a MOI of 1 demonstrated less than 5% survival (Table I). Cell survival was lowest in those cell lines with the shortest in vitro doubling times. NV1020 was more effective than G207 at killing AsPC cells after 2 days at all MOIs ($P < 0.01$). Doubling times of the four human pancreatic cancer cell lines examined are listed in Table I. The most rapidly dividing was HTB147 (30 hours) and the most slowly dividing was hs766t (72 hours). Tumor doubling time correlated with survival after infection with G207 or NV1020.

Viral Plaque Assays

Viral progeny production was quantified after infection with G207 or NV1020 in hs766t and HTB147, the cell lines with the longest and shortest doubling times, respectively. Both cell lines supported G207 and NV1020 viral proliferation (Fig. 2). From the initial MOI of 0.01, the ratio of virus to cells increased

Table I. Survival of human pancreatic cancer cell lines after 4 days of exposure to G207 or NV1020

Cell line	Histology	TD (hr)*	G207†			NV1020		
			MOI 0.01	MOI 0.1	MOI 1	MOI 0.01	MOI 0.1	MOI 1
HTB147	Adenocarcinoma	30	53 (±2)	31 (±3)	2 (±2)	32 (±12)	23 (±5)	3 (±2)
AsPC	Adenocarcinoma	48	85 (±23)	42 (±20)	4 (±1)	38 (±14)	5 (±3)	1 (±2)
PANC-1	Epithelioid carcinoma	57	71 (±14)	51 (±20)	27 (±2)	73 (±9)	64 (±3)	28 (±3)
hs766t	Adenocarcinoma	72	79 (±9)	71 (±8)	26 (±5)	71 (±13)	41 (±14)	23 (±7)

MOI = multiplicity of infection, which is the ratio of virus to cells.

*Cell line population doubling time measured in hours.

†Results are percentages ± standard deviation. All assays were performed in triplicate. Cells exposed to virus and cells in serum-free media were counted on a hemacytometer using trypan blue exclusion of nonviable cells. Survival of each cell line population was calculated as the average (n = 3) number of cells in treatment groups divided by the average (n = 3) number of cells in the control (medium only) wells.

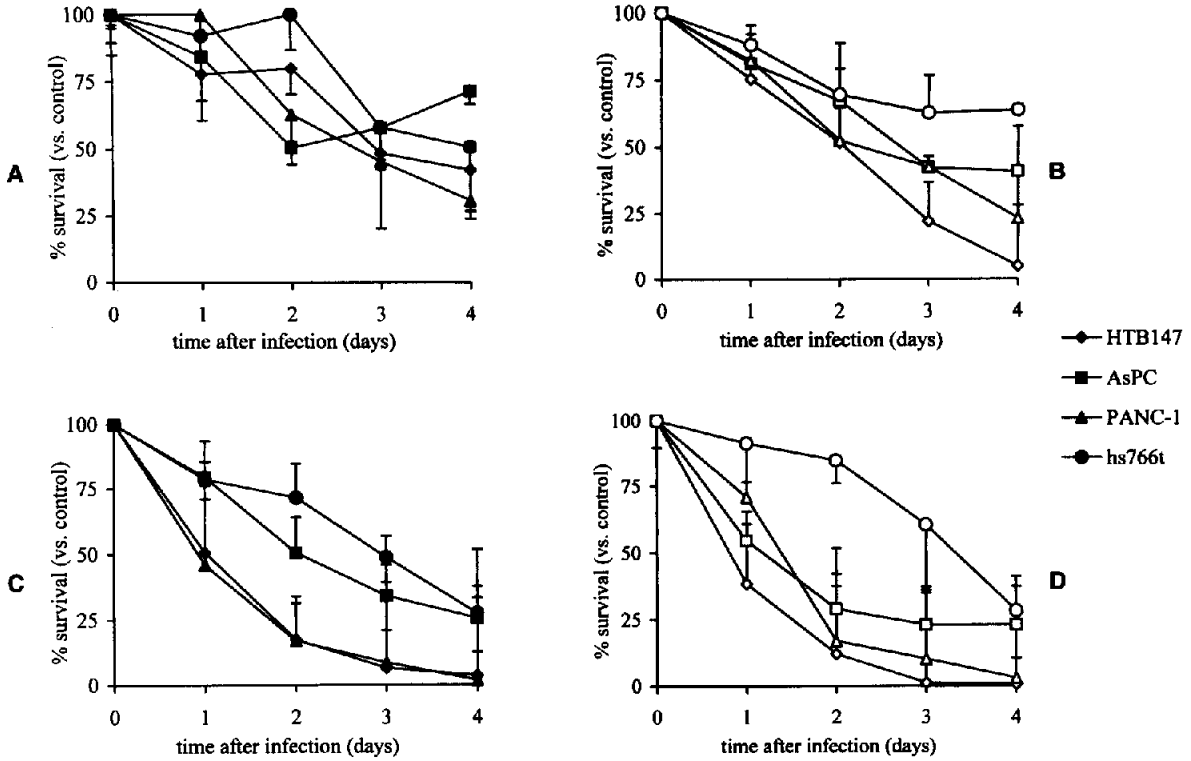

Fig. 1. Survival of four pancreatic cancer cell lines after exposure to G207 or NV1020. Survival assays were performed in triplicate on AsPC, hs766t, HTB147, and PANC-1. Cells were infected with G207 (black symbols) or NV1020 (white symbols) at MOIs of 0.01, 0.1, or 1, and were monitored each day for viability using trypan blue exclusion. Cell survival for each cell line was calculated by dividing viability in each treatment group by the viability in uninfected control wells and multiplying by 100%. Cell survival is plotted as a function of time for G207, MOI 0.1 **(A)**; NV1020, MOI 0.1 **(B)**; G207, MOI 1 **(C)**; and NV1020, MOI 1 **(D)**. MOI 0.01 is not shown. Survival of all cell lines after infection with G207 or NV1020 decreased compared to control values after 1 day of treatment (Student's *t* test, $P < 0.05$). MOI 1 was more effective at cell killing than MOIs of 0.1 and 0.01 in each cell line ($P < 0.05$). NV1020 was more efficient than G207 after 2 days in killing AsPC cells at all MOIs ($P < 0.01$).

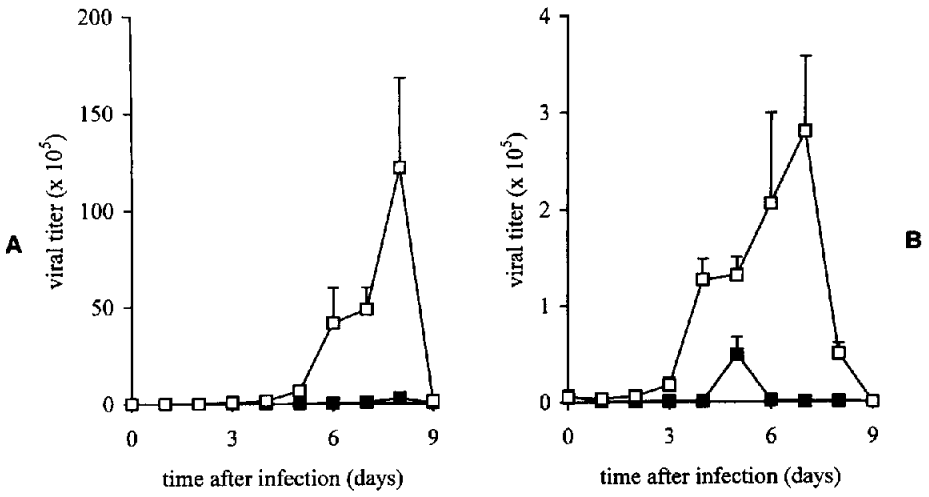

Fig. 2. Replication of G207 and NV1020 in hs766t **(A)** and HTB147 **(B)** pancreatic cancer cell lines after infection at MOI 0.01. Cell lysates and supernates from duplicate treatment wells were collected every 24 hours and titrated by standard plaque assay. Viral titer is plotted as a function of time. The peak viral titer was higher for NV1020 (white squares) than G207 (black squares) in both cell lines, by a factor ranging from 43 for hs766t to 6 for HTB147. From an initial MOI of 0.01 (5000 pfu), the ratio of G207 virus to cells increased 58 times for hs766t and 10 for HTB147. For NV1020, the maximum MOI increased 2444 and 56 times, respectively.

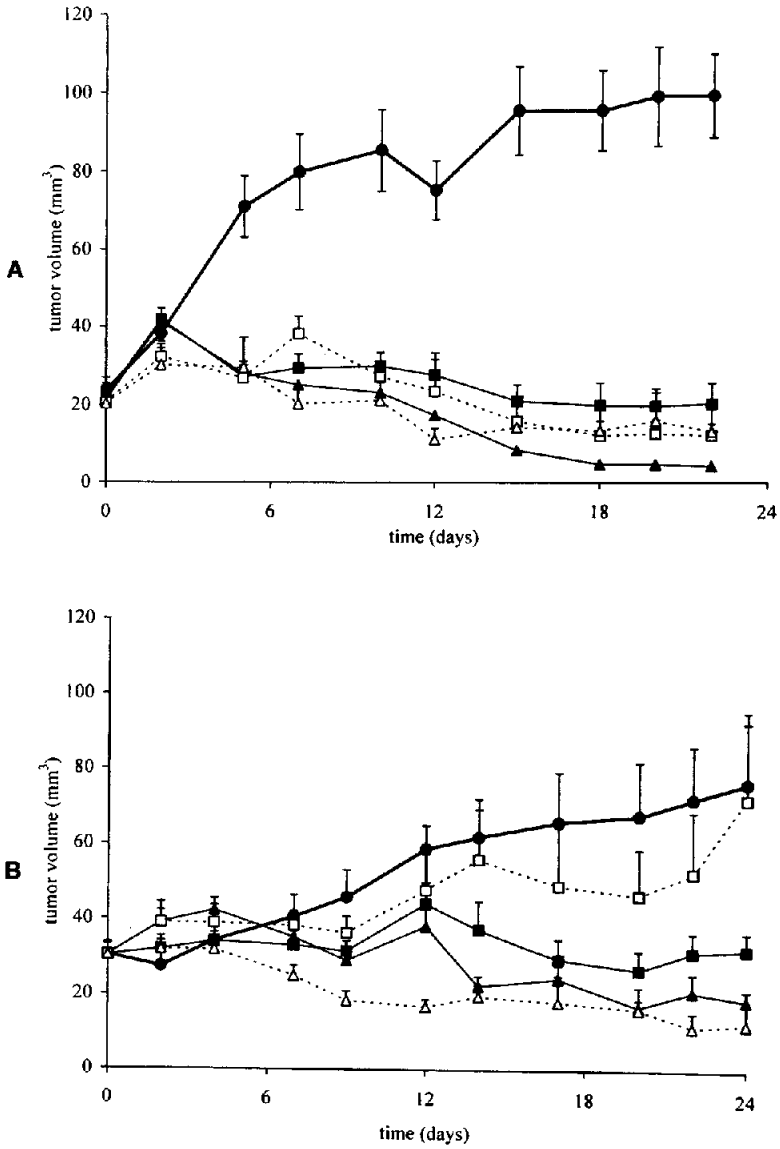

Fig. 3. Efficacy of direct intratumoral G207 or NV1020 injection in the treatment of hs766t **(A)** and HTB147 **(B)** pancreatic cancer flank tumors. At treatment, pancreatic cancer tumor volumes in athymic mice were 22 ± 3 mm^3 and 30 ± 3 mm^3 (± standard error of the mean) for hs766t and HTB147, respectively. Tumors were directly injected, in a volume of 0.075 ml, with either three doses of serum-free medium administered over 5 days (control, black circles), 1 × 10^7 pfu of G207 (G207 single-dose, black boxes), three doses of 1 × 10^7 pfu of G207 administered over 5 days (G207 three doses, black triangles), 1 × 10^7 pfu of NV1020 (NV1020 single-dose, white squares), or three doses of 1 × 10^7 pfu of NV1020 administered over 5 days (NV1020 three doses, white triangles). Duration of response was monitored for 3 weeks. Average tumor volume (± standard error of the mean) is plotted as a function of time. **(A)**, hs766t tumor volume in all treatment groups was decreased compared to control values ($P < 0.0002$). Tumors in the G207 three dose treatment groups were smaller than those in the respective single-dose treatment groups ($P < 0.02$). **(B)**, HTB147 tumor volume in the G207 treatment groups and the NV1020 three-dose group was decreased compared to control values ($P < 0.05$). Tumors in both three-dose treatment groups were smaller than those in their respective single-dose treatment groups ($P < 0.04$).

Table II. Mean tumor volume and proportion of nonpalpable tumor for each treatment group

Treatment group*	Mean hs766t volume†	Proportion with no hs766t tumor‡	Mean HTB147 volume†	Proportion with no HTB147 tumor‡
Control	99 ± 11	0/10	76 ± 16	0/10
G207 single-dose	20 ± 4§	1/10	32 ± 5§	0/10
G207 three doses	4 ± 2§	4/10	19 ± 3§	0/10
NV1020 single-dose	12 ± 3§	4/10	72 ± 23	0/10
NV1020 three doses	13 ± 6§	4/10	12 ± 5§	0/10

*hs766t tumors of 22 ± 3 mm^3 and HTB147 of 30 ± 3 mm^3 (± standard error of the mean) in athymic mice were directly injected with serum-free medium (control), 1×10^7 pfu of G207 (G207 single-dose), 1×10^7 pfu of NV1020 (NV1020 single-dose), three doses of 1×10^7 pfu of G207 administered over 5 days (G207 three doses) or three doses of 1×10^7 pfu of NV1020 administered over 5 days (NV1020 three doses). Duration of response was monitored for 3 weeks.

†Results are mean (n = 10 tumors per treatment group) tumor volume ± standard error of the mean.

‡Results are number of animals with nonpalpable tumors at the end of the experiment.

§Tumor volume in all treatment groups was decreased compared to control values ($P < 0.0002$ for hs766t, $P < 0.04$ for HTB147). For hs766t tumors, tumors in the G207 three-dose treatment groups were smaller than in the respective single-dose treatment group ($P < 0.02$). For HTB147 tumors, tumors in the G207 three-dose treatment groups and the NV1020 treatment groups were smaller than in the respective single-dose treatment groups ($P < 0.02$ and $P < 0.04$, respectively).

10 times for HTB147 and 58 times for hs766t. For NV1020, maximum MOIs increased 56 and 2444 times, respectively. In both cell lines, peak viral titer was higher for NV1020 than G207 by a factor ranging from 6 for HTB147 to 43 for hs766t.

Treatment of Flank Tumors in Athymic Rats and Mice

Efficacy of intratumoral viral injection in suppressing flank xenografts in athymic mice was measured. HTB147 and hs766t were chosen for the experiment because they had the shortest and longest in vitro doubling times, respectively. It should be noted that, although HTB147 had the shortest in vitro doubling time, it grew slowly in vivo, with a doubling time of 10 days, compared with 3 days for hs766t. At the end of treatment, average hs766t tumor volumes were as follows: control, 99 ± 11; G207 single-dose, 20 ± 5; NV1020 single-dose, 12 ± 3; G207 three doses, 4 ± 2; and NV1020 three doses, 13 ± 6 mm^3 (Fig. 3, *A*). The average HTB147 tumor volumes were as follows: control, 76 ± 16; G207 single-dose, 32 ± 5; NV1020 single-dose, 72 ± 23; G207 three doses, 19 ± 3; and NV1020 three doses, 12 ± 5 mm^3 (Fig. 3, *B*). Starting at 5 days (hs766t) and 9 days (HTB147) after treatment, tumor volume was lower in all treatment groups compared to control values ($P < 0.01$), with the exception of HTB147 tumors treated with NV1020 single-dose, which did not differ in size significantly from control values. Twenty-five percent (5 of 20) of hs766t tumors treated with G207 and 40% (8 of 20) treated with NV1020 were nonpalpable at 22 days after treatment (Table II). There was no complete response to viral treatment in HTB147 tumors. For hs766t, G207 three doses was more effective than G207 single-dose ($P < 0.02$), whereas both modes of NV1020 administration were equally effective (see Fig. 3, *A*). For HTB147, three-dose administration of each virus was more effective than the respective single-dose treatment ($P < 0.04$).

DISCUSSION

In order for a replication-competent oncolytic virus to be effective for cancer therapy, it must be able to infect the tumor cell of interest, replicate to produce progeny, and lyse the cells. This efficacy must then be balanced against the safety profile of the agent. G207 has been shown to be effective in a variety of malignancies, including glioma,[15] mesothelioma,[23] head and neck[16] and prostate[24] cancer cells, and metastases to the brain,[25] liver,[17] and peritoneum.[19] The efficacy of NV1020 has been described previously in head and neck cancers.[26] In pancreatic cancer cells the oncolytic properties of G207 have been described in vitro.[18] The current experiments extend these observations to another promising virus and also examine both viruses in vivo. The present study demonstrates that G207 and NV1020 effectively infect, replicate within, and kill human pancreatic cancer cells both in vitro and in vivo.

The results of these experiments suggest that the proliferate characteristics of the target cell predict the response to viral treatment. The relatively more rapidly growing pancreatic cancer cell lines AsPC and HTB147 had a greater response to both viruses than PANC-1 and hs766t in vitro. In other cell lines investigated in our laboratory, the efficacy of G207 also correlated closely with doubling time or S-phase frac-

tion.[16,17,19] However, the in vivo characteristics of tumors may be the most important determinants of clinical response to viral therapy. Although hs766t had a longer in vitro doubling time than HTB147, in vivo hs766t was the faster growing tumor and was more efficiently eradicated by both viruses compared to HTB147. The markedly higher viral proliferation in hs766t may account for the high number of complete responses seen with this cell line.

NV1020 produced higher quantities of viral progeny than G207. The presence of one functioning copy of the neurovirulence and replication efficiency $\gamma_1 34.5$ gene in NV1020, which apparently reduces dependence on the host cell for proliferation, may be responsible for this difference in viral growth.[18,28] In the hs766t cell line, NV1020 produced much higher viral titers than G207, but no difference was seen in the ability of each virus to kill hs766t tumors in vivo. This may be due to the efficient killing of hs766t tumors by both viruses. It may be that for a single sensitive cell line, maximum efficacy is achieved at a concentration of virus well below the amount achieved at peak production. Whether NV1020 is more efficient in humans, where tumors are more heterogeneous, requires further clinical investigation.

Since these viruses are replication competent, safety issues relating to viral dissemination and its impact in the host must be addressed. Both viruses were well tolerated by all animals. No animal inoculated with either virus showed morbidity or mortality from the virus, and they continued to eat and groom. All animals survived the experiment. Viral dissemination in normal murine tissues has been quantified previously by our laboratory using real-time quantitative polymerase chain reaction, and no evidence of viral proliferation has been observed in any organ after subcutaneous inoculation of virus.[17] In addition, the multiple mutations within the genome of these viruses make reversion to wild type unlikely. Both viruses retain the thymidine kinase gene, making them sensitive to acyclovir therapy if dissemination occurs. Furthermore, both viruses have been tested in nonhuman primates and have proved to be attenuated compared to wild-type strains.[29-31]

This study has several implications for potential clinical application of oncolytic HSV. In the adjuvant setting, when there may be viable tumor cells present in the resection bed but the tumor cell burden is low, delivery of sufficient virus to reach MOI of 1 to 100 would be feasible. Even with no further local proliferation of virus, such high effective doses of virus will likely kill residual tumor cells. This may be an ideal setting for the use of the more attenuated G207. On the other hand, for patients with large unresectable tumors, and for palliation, it will be important for local production of virus to occur so that progeny virus can enhance antitumor efficacy. In such situations, administration of NV1020 may be preferred, since its relatively higher proliferative rate may result in a higher effective dose at the tumor site.

CONCLUSION

Attenuated, replication-competent herpes simplex viruses G207 and NV1020 are effective at treating experimental human pancreatic cancer by intratumoral injection. Cell survival decreased after infection with each virus compared to control values, and both viruses were able to produce a burst of viral progeny that ranged from 10 to 2444 times the initial MOI. NV1020 had between 6 and 43 times higher viral progeny production than G207. Both viruses were effective at treating pancreatic cancer xenografts, particularly with a multiple-dose regimen. These viruses represent a new class of agents and a novel treatment approach to pancreatic cancer, which is largely resistant to standard therapy.

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Discussion

Dr. Douglas L. Fraker (Philadelphia, Pa.). Regarding neurotropism, are there data in primate models that are a more typical host of these herpes viruses or data that this totally eliminates the neurotoxicity? Could you speculate on how you would get around the problems of delivery in clinical pancreatic cancer, as well as on generation of host immunity?

Dr. Jarnagin. In preclinical toxicology studies, performed in Aotus monkeys that are exquisitely sensitive to wild-type herpes virus, the animals did not develop significant clinical neurologic toxicity. In previous experiments, when we used intraportal injections in a metastatic colon cancer model and then analyzed brain and other tissues by polymerase chain reaction, none of the tissues other than liver had evidence of viral gene presence. As far as delivery is concerned, it depends on the situation. For example, after tumor resection, viruses could conceivably be delivered through an intraperitoneal port or simply placed in the operative field. In a patient with an unresectable tumor, it would be a bit difficult to deliver viruses intra-arterially, but perhaps direct injection even endoscopically would be possible. In regard to host immunity, preformed antibodies to herpes viruses do not eliminate the ability of the viruses to kill cells in primate or mouse models.

Dr. John P. Hoffman (Philadelphia, Pa.). You implied from your introduction that we need better systemic therapies for pancreatic cancer. Have you used this metastatic model to determine whether or not the virus can go elsewhere?

Dr. Jarnagin. Not in pancreatic cancer, but in other models, yes we have. In colorectal cancer cell lines metastatic to the liver, we and others have shown that this is potentially effective, and perfusion of the portal vein with virus actually results in selective infection of the metastatic deposits within the liver.

Dr. S. Archer (Boston, Mass.). Do you have any idea what the mechanism of cytotoxicity is?

Dr. Jarnagin. It seems, looking at the histology, that it is mostly direct cell lysis. There is some evidence of apoptosis, although I do not know if that has been fully resolved.

Dr. Archer. Can you actually hook up a therapeutic transgene to these viruses to affect cell kill?

Dr. Jarnagin. There are now newer viral strains that are replication competent, oncolytic, and express high levels of various stimulatory genes, such as IL-12 and IL-2.

Transjugular Intrahepatic Portosystemic Shunt vs. Small-Diameter Prosthetic H-Graft Portacaval Shunt: Extended Follow-Up of an Expanded Randomized Prospective Trial

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We report herein the results of extended follow-up of an expanded randomized clinical trial comparing transjugular intrahepatic portosystemic shunt (TIPS) to 8 mm prosthetic H-graft portacaval shunt as definitive treatment for variceal bleeding due to portal hypertension. Beginning in 1993, through this trial, both shunts were undertaken as definitive therapy, never as a "bridge to transplantation." All patients had bleeding esophageal/gastric varices and failed or could not undergo sclerotherapy/banding. Patients were excluded from randomization if the portal vein was occluded or if survival was hopeless. Failure of shunting was defined as inability to shunt, irreversible shunt occlusion, major variceal rehemorrhage, hepatic transplantation, or death. Median follow-up after each shunt was 4 years; minimum follow-up was 1 year. Patients undergoing placement of either shunt were very similar in terms of age, sex, cause of cirrhosis, Child's class, and circumstances of shunting. Both shunts provided partial portal decompression, although the portal vein–inferior vena cava pressure gradient was lower after H-graft portacaval shunt ($P < 0.01$). TIPS could not be placed in two patients. Shunt stenosis/occlusion was more frequent after TIPS. After TIPS, 42 patients failed (64%), whereas after H-graft portacaval shunt 23 failed (35%) ($P < 0.01$). Major variceal rehemorrhage, hepatic transplantation, and late death were significantly more frequent after TIPS ($P < 0.01$). Both TIPS and H-graft portacaval shunt achieve partial portal decompression. TIPS requires more interventions and leads to more major rehemorrhage, irreversible occlusion, transplantation, and death. Despite vigilance in monitoring shunt patency, TIPS provides less optimal outcomes than H-graft portacaval shunt for patients with portal hypertension and variceal bleeding. (J GASTROINTEST SURG 2000;4:589-597.)

KEY WORDS: Portal hypertension, portal decompression, TIPS

Transjugular intrahepatic portosystemic shunt (TIPS) is embraced by many nonsurgeons as the "first-line" option when treating patients with variceal hemorrhage who have failed or are unable to undergo medical and endoscopic therapy. High utilization of TIPS is, undoubtedly, a consequence of many beliefs. TIPS can relieve portal hypertension and thereby abrogate variceal hemorrhage. TIPS can be undertaken with relative expedience and with acceptable periprocedural morbidity utilizing techniques familiar to many interventional radiologists. TIPS is a realistic bridge to hepatic transplantation.

Although acceptance of most new procedures generally requires documented equivalency or, better yet, superiority to comparable procedures, TIPS has been embraced without such comparisons. Specifically, the widespread acceptance of TIPS has occurred despite a lack of controlled comparisons to the "gold standard" of portal decompression, operatively constructed shunts. Seemingly, it is believed that TIPS is as efficacious as surgical shunts, and all patients with bleeding varices are potential candidates for hepatic transplantation. The latter belief is unrealistic and the former belief is unproved.

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Previously we reported results of a prospective randomized controlled clinical trial comparing TIPS to an operatively constructed small-diameter prosthetic H-graft portacaval shunt.[1] Furthermore, we reported the cost of care associated with each shunt through this protocol.[2] The purpose of the present report is to detail extended follow-up of an expanded form of the prospective randomized controlled clinical trial comparing TIPS to an operatively constructed small-diameter prosthetic H-graft portacaval shunt. Our hypotheses in undertaking this report were that each shunt would be associated with similar periprocedural morbidity and mortality and similar long-term failure rates and survival.

METHODS

In 1993, after institutional review board approval, we began to accrue patients with cirrhosis, portal hypertension, and variceal hemorrhage in a prospective randomized trial comparing TIPS to 8 mm prosthetic H-graft portacaval shunt. All patients had experienced bleeding from varices or gastropathy, and had failed or were not amenable to nonoperative therapy such as sclerotherapy or banding. Shunting was always undertaken as definitive therapy, never as a bridge to transplantation.

After initial evaluation, all patients underwent routine laboratory assessment including complete blood count, serum electrolytes, standard liver function tests, prothrombin time, partial thromboplastin time, and urinalysis. The severity of cirrhosis was staged by assigning a Child's class (A, B, or C) to each patient. By protocol, each patient underwent preshunt color-flow Doppler ultrasound imaging of the portal vein to determine portal vein patency and the quality and direction of portal blood flow. If there was uncertainty about the patency of the portal vein by color-flow Doppler ultrasound, a mesenteric angiogram with mesenteric venous phase return was obtained to evaluate the patency and quality of flow in the portal vein. After this evaluation and after informed consent was obtained, patients were randomized to undergo TIPS or 8 mm prosthetic H-graft portacaval shunt placement in pairs to allow for sequential analysis by pair differences. Those participants in the trial who gave their consent were blinded as to which shunt was next to be applied. Patients were not randomized only when the portal vein was thrombosed or chances of surviving shunting were thought to be hopeless because of profound ill health.

Encephalopathy was assessed as none, mild (controlled at home with a protein-restricted diet and lactulose), or severe (hospital admissions required despite therapy). Ascites was graded as absent, moderate (clinically evident, but well controlled with fluid restriction and oral diuretics), or severe (abdominal distention refractory to fluid restriction and maximal diuretic therapy, often requiring large-volume paracentesis or placement of a peritoneovenous shunt).

Circumstances of shunting were defined as elective (shunting scheduled for convenience in a hemodynamically stable patient), urgent (shunting undertaken within 24 hours of presentation), or emergency (shunting undertaken as soon as possible, certainly within 8 hours of presentation).

The technique used to construct the 8 mm prosthetic H-graft portacaval shunt has been described elsewhere.[3] As well, the technique that we used to construct the TIPS shunts has been described elsewhere.[1] Briefly, all TIPS were undertaken under general anesthesia. All TIPS but one were placed through a right internal jugular vein approach. Coaxial dilators were introduced into the superior vena cava and then advanced into the inferior vena cava over a guidewire. A 10 F introducer sheath was then advanced over the wire into the inferior vena cava. A 7 F multipurpose catheter (Cordis Corp., Miami, Fla.) was then advanced through the 10 F sheath into the right hepatic vein. Under fluoroscopic guidance, this catheter was advanced in the parenchyma of the right lobe of the liver until a major branch of the right branch of the portal vein was cannulated. Then the transhepatic tract was balloon dilated to 8 F and, ultimately, the balloon wire was exchanged out over a wire for a 10 mm × 68 mm Schneider Wallstent (Pfizer, Inc., New York, N.Y.). After appropriate positioning under fluoroscopic guidance, the Wallstent was deployed and then dilated up to 8 to 10 mm, or until an appropriate gradient between the portal vein and the hepatic vein, or inferior vena cava, was reached. Generally we sought a portal vein–inferior vena cava (PV-IVC) pressure gradient near 10 mm Hg, although a lesser gradient was acceptable.

The 8 mm prosthetic H-graft portacaval shunt was constructed using an external ring-reinforced polytetrafluoroethylene (PTFE) graft. All operations were begun with a right-sided transverse abdominal incision. Adequate exposure of the inferior vena cava was gained through a limited Kocher maneuver. The portal vein was exposed in the posterolateral hepatoduodenal ligament. The PTFE graft was cut with bevels at each end, 90 degrees to each other, and measured 3 cm long from toe to toe and 1.5 cm from heel to heel. A portion of the caudate lobe was generally excised to facilitate shunt placement. After placing a partially occluding clamp, a generous window was cut in the inferior vena cava. The graft was sewn end to side to the vena cava and then to the portal vein with running nonabsorbable monofilament sutures.

Measurements of portal vein pressures and inferior vena cava pressures were obtained, and calculations of the PV-IVC pressure gradients were undertaken before and after shunting. With shunting, a decrease in the portal vein pressure of more than 10 mm Hg and a postshunt PV-IVC gradient of less than 10 mm Hg were sought. Additionally, with the H-graft shunt, the presence of a thrill along the vena cava just cephalad to the graft helped confirm shunt patency.

Prior to discharge, shunt patency was documented near postshunt day 4 by transvenous cannulation of the shunt. This was undertaken transfemorally after H-graft portacaval shunt and transjugularly after TIPS. Portal vein pressures and inferior vena cava pressures were measured and PV-IVC pressure gradients were calculated. Direction and quality of portal flow were determined by venography and by color-flow Doppler ultrasound.

After TIPS, patients underwent color-flow Doppler ultrasound evaluation of their shunts at 6 weeks, 12 weeks, and 6 months, and every 6 months thereafter. Studies compatible with stent stenosis led to transjugular shunt assessment with interventions for increased gradients across the shunts. We have never been able to measure flow in the H-graft shunt using color-flow Doppler ultrasound. Therefore we have only used color-flow Doppler ultrasound for patients with H-graft shunts to evaluate portal vein flow. Patients were followed prospectively through semiannual clinic visits, with assessment of shunt patency and direction of portal blood flow by color-flow Doppler ultrasound. Abnormal results by color-flow Doppler ultrasound indicated the necessity for repeat venography.

Interval venography was undertaken routinely at 1 year, 3 years, 5 years, and 10 years after H-graft shunt and TIPS to measure gradient pressures, assess shunt patency, and grade portal flow.

All patients are accounted for, with follow-up within the last year for all patients, unless otherwise noted. Follow-up after shunting ranged from 1 to 6 years, with minimum follow-up of more than 1 year. Median follow-up was 4 years after each shunt. Average follow-up after H-graft shunt is 3.8 ± 1.7 years and after TIPS is 3.6 ± 1.5 years over 4 years.

Shunt failure was defined as inability to complete shunting, irreversible shunt occlusion, major variceal rehemorrhage, liver failure requiring transplantation, or death. Data are presented as average ± standard deviation (SD) when appropriate. All data are stored in a file-based registry (dBase IV, Borland International, Inc., Borland, Tex.). Statistical comparisons were undertaken using True Epistat (Epistat Service, Richardson, Tex.). When chi-square testing was used, the method specific for prospective trials was used. Statistical significance was assigned with 95% probability.

RESULTS

Patient Demographics

One hundred thirty-two patients, 91 males and 31 females, underwent randomization. Sixty-six patients underwent 8 mm prosthetic H-graft portacaval shunt placement and 66 patients underwent TIPS. Mean age for patients undergoing H-graft portacaval shunting was 54 ± 13 years, and mean age for patients undergoing TIPS was 55 ± 12.5 years (Table I).

For patients undergoing TIPS, cirrhosis was due to alcohol abuse (60%), viral hepatitis (7%), both alcohol abuse and viral hepatitis (10%), idiopathic causes (20%), and alpha-1 antitrypsin deficiency (3%). For patients undergoing small-diameter prosthetic H-graft shunting, alcohol was responsible for cirrhosis in 66% of patients, hepatitis virus in 6%, both alcohol and hepatitis in 11%, unknown causes in 14%, and methotrexate in 3%. Among TIPS patients, 12 (18%) were Child's class A, 25 (38%) were Child's class B, and 29 (44%) were Child's class C. Among H-graft shunt patients, nine (14%) were Child's class A, 24 (36%) were Child's class B, and 33 (50%) were Child's class C (see Table I).

Before TIPS, ascites was present in 70% of patients. In these patients, ascites was moderate in 80% and severe in 20%. In patients undergoing H-graft portacaval shunt placement, ascites was present in 68% of the patients. In these patients, ascites was

Table I. Comparison of demographic data of patients randomized to undergo TIPS or 8 mm prosthetic H-graft portacaval shunt

	TIPS	H-graft shunt
No. of patients	66	66
Mean age ± SD (yr)	55 ± 12	54 ± 13.5
Sex (M/F)	20/46	25/41
Ascites (%)	70	68
Encephalopathy (%)	29	18
Child's class		
A	12	9
B	25	24
C	29	33
Etiology of cirrhosis		
Alcohol (%)	60	66
Viral (%)	7	6
Both (%)	10	11
Idiopathic (%)	20	14
Other (%)	3	3

TIPS = transjugular intrahepatic portosystemic shunt.

Table II. Portal vein pressures and portal vein–inferior vena cava pressure gradients before and after TIPS or 8 mm prosthetic H-graft portacaval shunt

	TIPS (mm Hg)	H-graft shunt (mm Hg)
Preshunt PV pressure	33 ± 7.8	30 ± 6.4
Preshunt PV-IVC pressure gradient	17 ± 5.2	16 ± 4.3
Postshunt PV pressure	27 ± 7.3*†	20 ± 5.8*
Postshunt PV-IVC pressure gradient	9 ± 4.1*†	5 ± 3.0*

PV = portal vein; PV-IVC = portal vein–inferior vena cava.
*Less than preshunt, $P < 0.01$, paired Student's t test.
†Greater than after 8 mm prosthetic H-graft portacaval shunt, $P < 0.01$, Student's t test.

moderate 85% and severe in 15%. Encephalopathy was present in 29% of patients before TIPS and in 18% of patients before H-graft shunt. Prior to TIPS, encephalopathy was graded as moderate in 89% and severe in 11%. For patients undergoing H-graft shunt, encephalopathy was moderate in 92% of patients and severe in 8%.

In patients undergoing TIPS, indications for shunting were bleeding from esophageal varices in 45% of patients, from gastric varices or gastropathy in 12%, and from both esophageal and gastric varices in 43%. In patients undergoing H-graft portacaval shunt placement, refractory hemorrhage occurred from esophageal varices in 58% of patients, from gastric varices or gastropathy in 10%, and from both esophageal and gastric varices in 32%. Seventy-eight percent of patients underwent TIPS as an elective procedure, 10% as an urgent procedure, and 12% as an emergency. H-graft portacaval shunting was undertaken as electively in 74% of patients, urgently in 14%, and as an emergency procedure in 12%.

Pressure Measurements

Partial portal decompression attained through TIPS or 8 mm prosthetic H-graft portacaval shunts resulted in significant decreases in portal pressures and PV-IVC pressure gradients ($P < 0.001$, paired Student's t test) (Table II). Portal pressures and PV-IVC pressure gradients were lower after 8 mm prosthetic H-graft portacaval shunts than after TIPS ($P < 0.01$, Student's t test) (see Table II).

Inability to Complete the Shunt

In two patients undergoing TIPS, the shunt could not be placed. One of the patients died 10 days after the attempt at shunting and the other was lost to follow-up (Table III). In each of these TIPS patients, the shunt could not be placed because the liver was too hard to advance a wire from the hepatic venous system into the portal venous system.

Table III. Comparison of occurrences of failure after TIPS or 8 mm prosthetic H-graft portacaval shunt

	TIPS	H-graft shunt
Could not place shunt	2	0
Irreversible shunt occlusion	4	2
Major variceal rehemorrhage	11*	2
Liver transplantation	5*	0
Death	29	20
Total number of failures	51†	24‡
Number of patients failing	42§	23

*Greater than after H-graft portacaval shunt, $P < 0.01$, log-likelihood ratio test.
†Forty-two patients experienced 51 occurrences of failure after TIPS.
‡Twenty-three patients experienced 24 occurrences of failure after H-graft portacaval shunt.
§Greater than after H-graft portacaval shunt, $P < 0.01$, Fisher's exact test.

Shunt Thrombosis

Shunt stenosis and thrombosis occurred in more patients ($P < 0.01$, Fisher's exact test) and with greater frequency ($P < 0.01$, Student's t test) after TIPS. Forty-nine interventions (balloon angioplasty, placement of another stent, thrombectomy, and/or embolectomy) were necessary to maintain patency or function in 19 (28%) of 66 patients after TIPS, and six interventions were necessary to maintain shunt patency or function in 5 (7.5%) of 66 patients after H-graft portacaval shunt. After TIPS, eight patients underwent one shunt revision, three underwent two shunt revisions, two underwent three shunt revisions, three underwent four shunt revisions, one underwent five shunt revisions, and two underwent six shunt revisions. After H-graft portacaval shunt, five patients required one intervention and one patient required two interventions to reestablish graft patency or correct shunt stenosis. One patient required operative revision of an occluded shunt before discharge 5 days after portacaval shunting. The other patients presented with shunt stenosis or occlusion at later follow-up and were managed with radiologic balloon dilation.

Irreversible shunt occlusion occurred in four patients after TIPS and in two patients after H-graft portacaval shunt (see Table III). Occlusion of the two H-graft shunts was noted at routine late-interval follow-up transfemoral shunt evaluation.

Major Rehemorrhage

Major recurrent bleeding occurred in 11 (16%) of 66 patients after TIPS and in 2 (3%) of 66 patients after H-graft portacaval shunt ($P < 0.01$, log-likelihood ratio test) (see Table III). Among these patients, recurrent major variceal hemorrhage within 30 days after TIPS occurred in two patients. In both patients, rebleeding was due to stent occlusion. One patient after H-graft shunt presented with recurrent hemorrhage early after shunting, and rehemorrhage was due to alcohol gastropathy. Nine patients had recurrent gastrointestinal hemorrhage late after TIPS, and in all instances bleeding was related to shunt occlusion or stenosis. Late rebleeding occurred in one patient after H-graft shunt, a consequence of alcohol gastropathy.

Postoperative Ascites and Encephalopathy

Ascites persisted more than 30 days after TIPS or H-graft shunts in 60% of patients with preoperative ascites. At late follow-up, 40% of patients with preshunt ascites who underwent TIPS and 28% of patients who underwent H-graft portacaval shunt continued to have ascites, which was generally mild and well controlled. The H-graft shunt subjectively seemed to better palliate ascites.

Early postshunt encephalopathy was difficult to quantify and determine because of general anesthesia and narcotic analgesia. Within 30 days after TIPS, 53% of patients with some degree of preshunt encephalopathy died of liver failure. No occurrences of new-onset encephalopathy were reported early after TIPS. Similarly, 50% of patients who presented with encephalopathy before H-graft portacaval shunt died within 30 days of surgery, always because of liver failure. Mild new-onset encephalopathy occurred in two patients after H-graft portacaval shunt.

Liver Transplantation

Five patients (7.5%) required liver transplantation after TIPS because of progressive postshunt liver failure (see Table III). At the time of TIPS placement, two patients were Child's class A, two were class B, and one was class C. After TIPS, each patient demonstrated progressive fatigue with deterioration of measurable liver function. The patient in Child' s class C underwent liver transplantation early after TIPS, whereas the other patients underwent transplantation at 2, 3, 4, and 5 years after TIPS. None of the patients who had H-graft portacaval shunts placed underwent transplantation after shunting. Liver transplantation was more frequent after TIPS ($P < 0.01$, log-likelihood ratio test).

Perioperative Mortality

Ten patients (15%) died within 30 days after TIPS. Seven patients were Child's class C and three patients were Child's class B. Liver failure was the cause of death in 9 of 10 patients. Recurrent variceal bleeding was the cause of death in one patient. Of the patients undergoing H-graft shunting, 13 (20%) died within 30 days of shunting ($P = 0.64$, chi-square test, when compared to mortality after TIPS). Eleven patients were Child's class C, one was Child's class B, and one was Child's class A. Early death was related to liver failure in 92% of these patients. One patient (8%) died on the day of shunting from respiratory insufficiency due to self-extubation and our inability to subsequently secure an airway.

Overall Mortality

Including early and late deaths, 20 patients (30%) died after H-graft shunt and 29 (43%) died alter TIPS ($P = 0.14$, chi-square test) (see Table III). Perioperative mortality was detailed previously. After H-graft portacaval shunt, seven patients died beyond 30 days after shunting. Liver failure was the cause of death in six patients, and the other patient died of colon cancer. One patient was Child's class A, three were Child's class B, and three were Child's class C.

After TIPS, there were 19 deaths beyond 30 days after shunting. Four patients were Child's class A, six were class B, and nine were class C. Fourteen patients died of liver failure, two patients died of massive recurrent gastrointestinal hemorrhage, and three patients died of malignancy.

Late mortality was greater after TIPS than after H-graft shunt (7 of 53 vs. 19 of 56, $P < 0.01$, chi-square test). If patients dying late of causes unrelated to their cirrhosis are eliminated from consideration, late mortality after TIPS was still greater than after H-graft shunts (6 of 52 vs. 16 of 53, $P < 0.03$, chi-square test).

Overall Failure Rate

A total of 42 patients (64%) experienced 51 occurrences of failure after TIPS, whereas 23 patients (35%) failed after H-graft portacaval shunting, experiencing 24 occurrences of failure (see Table III). Fail-

ure was more common after TIPS ($P < 0.002$, chi-square test).

DISCUSSION

The optimal management of patients with cirrhosis and portal hypertension presenting with variceal hemorrhage after failure of, or an inability to apply, sclerotherapy or banding remains debated. Many reports have documented the efficacy and liabilities, such as shunt stenosis and occlusion and postshunt liver failure, of TIPS.[4-6] A large number of physicians continue to use TIPS as first-line therapy in the definitive management of complicated portal hypertension despite a lack of clear documentation of *relative* efficacy and liability. We undertook this trial to establish the relative efficacy and liabilities of TIPS using an operatively constructed nonselective shunt, which by design also provides partial portal decompression. This report details the results of extended follow-up of an expanded prospective randomized controlled trial comparing TIPS to an 8 mm prosthetic H-graft portacaval shunt, both used as definitive therapies for variceal hemorrhage.

The patients in this trial were generally older men with advanced stages of cirrhosis. Alcohol was the cause of cirrhosis in more than two thirds of the patients. Esophageal varices were the sole cause of bleeding in half of the patients, and in the other half esophageal varices were often associated with gastric varices or gastropathy. All patients were candidates for sclerotherapy and/or banding and either failed such therapy or the therapy could not be applied prior to randomization and shunting. Ascites was present before shunting in nearly two thirds of the patients, although it was generally controlled with dietary restrictions and oral diuretics. A very small number of patients required large-volume paracentesis preoperatively. Preoperative encephalopathy was present in less than 30% of patients, and it was generally controlled with dietary restrictions and medical therapy. Improvements in our care of patients with portal hypertension and bleeding varices through improvements in ICU care and sclerotherapy/banding resulted in shunting being increasingly undertaken under elective circumstances and less often as emergencies. In summary, patients undergoing placement of either type of shunt were similar in terms of age, sex, cause of cirrhosis, presence and severity of ascites and encephalopathy, Child' s classification, and urgency of shunting.

Patients in this trial were randomized in pairs to allow for sequential analysis by pair differences. When we began this trial, the relative efficacies and liabilities of TIPS and small-diameter prosthetic H-graft portacaval shunt were completely unestablished. Therefore this trial design was chosen to avoid enrolling an insufficient or excessive number of patients. It might seem that randomization in pairs would allow for bias in assigning therapy, but great effort was undertaken to ensure that those participants from whom consent was obtained were blinded as to the next shunt type to be assigned. As well, the similarity between the groups of patients undergoing either TIPS or H-graft shunt placement attests to the random nature of shunt assignment.

Failure to complete shunting has been noted since the first reports introducing TIPS in the late 1980s.[4,5] In only a small number of our patients was TIPS not accomplished because of technical difficulties. Both instances related to the inability to provide an intrahepatic tract to deploy the wall stent.

The ability of partial portal decompression to control variceal bleeding has been previously reported by many.[5,7-9] In this trial, both TIPS and the 8 mm prosthetic H-graft portacaval shunt achieved partial portal decompression, significantly reducing portal pressures and PV-IVC pressure gradients. As would be expected, both types of shunts controlled variceal hemorrhage, particularly in the periprocedural period. Although both shunts decreased portal pressures and PV-IVC pressure gradients, the prosthetic H-graft portacaval shunt was more effective in doing so. As might be expected, this translated into improved control of variceal bleeding. Longer term, increased rates of stenosis and occlusion of the TIPS shunts resulted in loss of partial portal decompression and, as again would be expected, higher rates of variceal rehemorrhage.

Partial portal decompression attained through TIPS or H-graft portacaval shunt resulted in improvement of ascites. Few patients after either shunt presented with refractory ascites requiring large-volume paracentesis or peritoneovenous shunts, although the small-diameter prosthetic H-graft shunt seemed more efficacious than TIPS in controlling ascites.

Although admittedly difficult to quantify, preshunt encephalopathy was an ominous sign. More than half of the patients who died perioperatively after shunting had signs of encephalopathy before shunting. The majority of these patients died of liver failure. Encephalopathy was a moderate problem after TIPS or small-diameter prosthetic H-graft shunt, although it occurred in only two new patients. Similarly, others have reported low rates of new-onset postshunt encephalopathy after partial portal decompression attained through surgical shunts.[7] Long-term encepha-

lopathy after TIPS is generally reported to be higher, around 20%.[4,5] It generally occurs early after shunting and is thought to be treatable with dietary restrictions and oral or rectal lactulose. Occasionally encephalopathy develops late with progressive hepatic dysfunction and becomes chronic, requiring frequent hospital admissions.

Recurrent variceal bleeding occurred more frequently after TIPS than after small-diameter H-graft portacaval shunt. After TIPS, recurrent variceal bleeding was almost always associated with shunt stenosis or occlusion, which required, and was generally amenable to, radiologic interventions to restore patency and function.

The incidence of shunt stenosis was higher after TIPS than after H-graft shunt. After TIPS almost one third of patients required radiologic intervention to maintain or restore TIPS shunt function or patency. Generally the incidence of shunt stenosis and occlusion after TIPS is reported to be near 50%,[4,5] although the actual incidence will vary depending on the length and scrutiny of follow-up and survival. Several patients required more than one intervention due to recurrent shunt stenosis or thrombosis.

Stenosis and occlusion after TIPS are generally a result of technical problems such as kinking of the stent, incorrect stent placement, or foreshortening of the stent. Other factors may also play a role. In this trial, shunt stenosis and occlusion after TIPS were responsible for serious morbidity, such as variceal rehemorrhage, and thereby led to considerable interventions, such as blood transfusions, ICU care, shunt revisions, and prolonged and expensive hospital care, with increased mortality. Shunt stenosis and occlusion after TIPS and vigilance to maintain shunt patency represent major drawbacks to TIPS.

After H-graft portacaval shunting, alcohol-induced gastritis played the major role in the reoccurrence of gastrointestinal hemorrhage. Previously we reported social misbehaviors characteristic of patients with alcoholic cirrhosis, such as reckless driving and continuous alcohol binging, and how they can affect survival after portacaval shunting.[10]

Stenosis occurred late in a small number after H-graft shunt and was well managed by radiologic dilation. Shunt occlusion after H-graft portacaval shunt was quite uncommon. Early after H-graft shunting, occlusion occurred uncommonly and required operative revision. As well, late H-graft shunt occlusion was very uncommon and irreversible by radiologic intervention. Other surgeons reporting on the small-diameter H-graft portacaval shunt have also documented very low rates of shunt stenosis and occlusion.[7,9]

Overall, at a median follow-up of 4 years, more patients died after TIPS than after small-diameter prosthetic H-graft shunt, particularly late after shunting. Although the H-graft shunt was associated with a higher number of perioperative deaths, late follow-up noted that significantly more patients who underwent TIPS died of liver failure or required liver transplantation to prevent certain death due to liver failure. One patient required transplantation early after TIPS and four other patients underwent transplantation late after TIPS. After H-graft shunt, no patients underwent liver transplantation. Progressive hepatic deterioration after TIPS is presumably a consequence of extensive loss of nutrient hepatic blood flow following TIPS.[11] Such loss of nutrient blood flow does not occur after H-graft shunting.[11-14] High death rates after TIPS certainly limited the occurrences of late stent stenosis and occlusion and variceal rehemorrhage, thereby limiting costs associated with TIPS.

The number of deaths in this trial seems high, although in line with other series. This death rate reflects the lack of selection of patients entered into this "all comers" trial. Only a hopeless prognosis prevented patients with patent portal veins from being enrolled in this trial. Possibly the lack of selectivity in entering patients into this trial limits the applicability of this trial. Certainly patients with better hepatic reserve would have done better, possibly obscuring differences between the shunts. However, the patients enrolled in this trial are the types of patients we see, and this trial gives us meaningful and realistic information on which to base future decisions. Furthermore, better patient selection, which promotes survival, would allow for follow-up of longer duration and thereby presumably more TIPS stenoses and occlusions and more resultant variceal hemorrhage.

The number of occurrences of shunt failure and the number of patients failing after TIPS were significantly greater than after small-diameter prosthetic H-graft portacaval shunt. Failure was generally a result of shunt stenosis/occlusion or hepatic deterioration. Critical appraisal of this trial might suggest that the definition of failure used was too restrictive or rigid. Death is certainly a fair and objective end point, although it can be due to causes other than considerations at hand. This has been noted in the Results and the Discussion sections of our report. Similarly, no one could well debate inability to place a shunt as a cause of failure. This specific cause of failure was uncommon in this trial, which is in line with other series. Liver transplantation was unexpected, given the design of the trial, and was applied to prevent death. Some might consider recurrent variceal hemorrhage to be less than a failure of shunting. Then what is it, if

not a failure? Recurrent variceal hemorrhage is certainly a life-threatening event, as a few patients having undergone TIPS in this trial can attest. Until recurrent variceal hemorrhage becomes a trivial event, it seems reasonable to consider it a failure of therapy designed to treat portal hypertension and bleeding varices.

In conclusion, this prospective randomized trial comparing TIPS to small-diameter prosthetic H-graft shunt in the treatment of complicated portal hypertension documents that TIPS is less effective than H-graft portacaval shunt if used as definitive therapy for variceal hemorrhage refractory to or not amenable to sclerotherapy or banding. Furthermore, shunt stenosis or occlusion occurring after TIPS was responsible for increased morbidity, such as recurrent gastrointestinal hemorrhage, and required, for many patients, multiple revisions to restore or maintain shunt patency and function. Additionally, TIPS, relative to the H-graft portacaval shunt, more frequently resulted in liver failure leading to liver transplantation or death.

Comparing TIPS to the H-graft portacaval shunt is most appropriate. Both achieve partial portal decompression. Neither is contraindicated for patients with ascites or hepatofugal portal flow. Their comparison is a true "apples to apples" comparison. Furthermore, given the results of this trial and what we now know about TIPS, it would seem most inappropriate to compare TIPS to any shunt best applied to patients in Child's class A.

This expanded trial with extended follow-up makes it difficult to support the routine application of TIPS as a "first-line" treatment option in the definitive management of variceal hemorrhage for patients with cirrhosis and portal hypertension who have failed sclerotherapy or banding. The role of TIPS should be confined. All would agree that patients with complicated portal hypertension and poor hepatic reserve who are awaiting liver transplantation should undergo TIPS, when necessary, as a "bridge" to transplantation. TIPS is also indicated for patients who are considered excessively high risk for intra-abdominal operations. TIPS, as well, seem better tolerated than H-graft shunts in patients with mitral regurgitation and aortic stenosis, both of which are not uncommon comorbidities in our experience.

The small-diameter prosthetic H-graft portacaval shunt is preferred as a "first-line" option in treating complicated portal hypertension. It is very efficacious in controlling variceal bleeding, carries relatively minimal risks of postshunt encephalopathy and hepatic failure, and has excellent long-term rates of patency.

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Discussion

Dr. Layton F. Rikkers (Madison, Wis.). I would like to congratulate you on an ambitious undertaking and for doing it so well. With many patients with portal hypertension undergoing TIPS in various hospitals, leaving so many fewer to enter such a trial, conducting a study such as this is a real challenge. Randomizing patients to nonoperative vs. operative therapy is particularly difficult. As you know, another trial of TIPS vs. distal splenorenal shunt is in progress, under the guidance of Dr. Mike Henderson. Among five institutions over several years, we have been able to randomize 110 patients, and you have exceeded that in a single institution.

Many of us worry about a high rate of thrombosis on long-term follow-up with the small-diameter H-graft. In your study, you evidently have very good long-term follow-up using angiograms, the longest follow-up being 7 years, with a very low rate of thrombosis, so it appears that the interposition prosthetic graft is viable long term, which was not the case with the large-bore interposition graft.

The gradient across your H-graft shunt was only 5 mm. The procedure was developed to be a partial shunt. Is it truly a partial shunt? How can you have such a low gradient and still maintain any portal perfusion of the liver? I realize that some residual intestinal venous hypertension may have benefits having to do with absorption of nutrients and avoidance of encephalopathy, but is this truly a partial shunt or is it a nonselective shunt?

Dr. Rosemurgy. I think it is both a nonselective shunt and a partial shunt. An earlier paper of yours, written in 1983, in which you discussed what happens after a distal splenorenal shunt, is of interest. As you know, after a distal splenorenal shunt, pressure can increase in the portal vein, it can remain the same, or it can decrease. If it increases, ascites can develop along with shunt thrombosis or portal vein thrombosis, and if it decreases, it never decreases to normal and the end result is the ascites is treated and there is a very good functional outcome. To me, that is partial portal decompression. I think it is easier to achieve with an H-graft portacaval shunt. Having said that, the goal of portal decompression should be to maintain a more normal pressure gradient between the portal vein and the inferior vena cava—not to reduce the gradient to zero, but to bring it down to a more physiologic number. In general, that number is five and the standard deviation is very low. We could certainly perform a TIPS procedure such that the gradient would be lower, but with the incidence of progressive hepatic deterioration being so high after TIPS, my fear is that if the TIPS was wider, for example, 10 or 12 mm in diameter, the incidence of failure and death would be even higher than it is. Clearly, hemodynamically TIPS are very different from H-graft shunts. We have looked at effective hepatic blood flow following these operations, and hepatic blood flow is preserved to a much greater degree following an H-graft shunt than it is with TIPS. That is confusing to me, because the perfusion in the liver after an H-graft shunt is being maintained better, even though the gradient in the portal system is lower.

Dr. Scott Helton (Chicago, Ill.). I also commend you on what I believe is now the largest prospective randomized trial reported on this topic. You had a large number of patients with Child's class C cirrhosis that you randomized; can you comment on what your outcome is in that group? Second, I know that you monitor resource utilization and cost, and you have published that information previously. Can you tell us about cost when patients were stratified by their Child's class? In our series, we recently reported that it is the Child's class A patients randomized to TIPS who are ordinarily the ones who have subsequent occlusion, and they are the major consumers of resources because of rebleeding.

Dr. Rosemurgy. In terms of short-term mortality, the differences by Child's class are not striking, but when long-term survival curves are examined, the gap begins to widen. Although late mortality is much higher following TIPS than after H-graft shunt, what is even more pronounced is the duration of survival. The patients who died after TIPS tended to die early after their operations, particularly those in Child's class C, whereas patients with H-graft shunts live longer, so the survival curves are very different.

If TIPS is used in Child's class C patients, progressive hepatic deterioration occurs quite rapidly. This results in low resource utilization but is not a good outcome.

Dr. James Sarfeh (Irvine, Calif.). I would like to address the issue of portal pressure gradients, which was raised by Dr. Rikkers. If portal pressure is measured as soon as the shunt placement is completed, the pressure is usually fairly low. It is probably low because the portal vein has been clamped, there is lactate buildup, and all sorts of vasoactive mediators have been released. This does not give you a good idea of what the real pressure is when the patient is recovered from the operation. I stopped measuring pressure intraoperatively. But if the pressure is measured when the patient is recovering and about to leave the hospital, you will find that the average gradient is 12 mm Hg and that is, in fact, a partial shunt.

Dr. Rosemurgy. We have measured the pressure gradient prior to discharge, and it averages 8 mm Hg. Some of the differences might be a result of our technique of shunt construction. We use a shorter graft than Dr. Sarfeh.

Dr. John Wong (Hong Kong). In your 1996 publication in *Annals of Surgery*,[1] you stated that it seems difficult to support TIPS in the treatment of bleeding varices. So why did you continue?

Dr. Rosemurgy. I believe I meant the "routine" application of TIPS. Since there is a great deal of support for TIPS, we thought we should continue the study. At that time, we had randomized only 64 patients, and our follow-up was really quite short. The median follow-up is now 4 years, and the average follow-up for these patients is just a little bit less than 4 years. I believe that it was important to study a large series of patients that have been randomized and well studied so that the point becomes irrefutable that, in fact, TIPS should not be routinely used in patients with bleeding varices.

Ten and More Years After Vertical Banded Gastroplasty as Primary Operation for Morbid Obesity

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Long-term follow-up (>10 years) after vertical banded gastroplasty (VBG) is almost nonexistent. The aim of this study was to determine long-term outcome after VBG in a group of 71 patients studied prospectively. Seventy-one consecutive patients with morbid obesity (54 women and 17 men; mean age 40 years [range 22 to 71 years]) underwent VBG from 1985 to 1989 and were followed prospectively. Follow-up was obtained in 70 (99%) of the 71 patients. Weight (mean ± standard error of the mean) preoperatively was 138 ± 3 kg and decreased to 108 ± 2 kg 10 or more years postoperatively. Body mass index decreased from 49 ± 1 to 39 ± 1. Only 14 (20%) of 70 patients lost and maintained the loss of at least half of their excess body weight with the VBG anatomy. Vomiting one or more times per week continues to occur in 21% and heartburn in 16%. Fourteen patients have undergone conversion from VBG to Roux-en-Y gastric bypass (11 patients) or other procedures (3 patients) because of a combination of inadequate weight loss in 13 patients, gastroesophageal reflux in five, and frequent vomiting in four. Only 26% of patients after VBG have maintained a weight loss of at least 50% of their excess body weight; 17% underwent bariatric reoperation with good results. Thus VBG is **not** an effective, durable bariatric operation. (J GASTROINTEST SURG 2000;4:598-605.)

KEY WORDS: Morbid obesity, bariatric surgery, vertical banded gastroplasty

Patients with morbid obesity have markedly increased mortality and morbidity.[1-3] Successful bariatric surgery has been proved to reduce weight and associated comorbid conditions such as diabetes mellitus, hypertension, hyperlipidemia, and sleep apnea[4-8] and has become an accepted therapy in selected patients. Indeed, a National Institutes of Health (NIH) Consensus Conference has "sanctioned" bariatric surgery as an accepted, effective approach.[9]

Currently there are two primary NIH-"sanctioned" operative approaches—vertical banded gastroplasty[10] and Roux-en-Y gastric bypass.[11] Our experience with nonbanded gastroplasty proved disappointing because of unsatisfactory maintenance of weight loss.[12] Vertical banded gastroplasty (VBG) was therefore chosen by us as our primary operation in 1985, again as a purely restrictive procedure with no gastrointestinal "bypass." Follow-up after up to 4 years revealed disappointing results as well[13]; after 3 years only 38% of patients maintained their weight after an initial loss of more than 50% of excess body weight (EBW), 30% of the patients continued maladaptive eating with vomiting one or more times a week, and 38% had symptomatic heartburn. Therefore, in 1989, we changed our primary operation to the Roux-en-Y gastric bypass (RYGB). Our patients have experienced satisfactory results with this operation; 70% have maintained a weight loss of ≥50% EBW.[4] Our aim in this study is to present the prospectively collected data from our VBG patients 10 and more years after the initial operation. Little data exist on long-term follow-up (>7 years) after

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VBG. We wanted to determine the success of VBG as defined by the following: (1) no need for reoperation because of VBG-related problems and (2) maintenance of loss of at least 50% EBW with VBG anatomy. Also, our goal was to evaluate outcome of patients who maintained a VBG anatomy for at least 10 years in terms of weight loss, gastrointestinal symptoms, and subjective quality of life.

PATIENTS AND METHODS

Clinical Material

From July 1985 through July 1989, 73 consecutive patients with morbid obesity (55 women and 18 men; mean age 40 years [range 22 to 71 years]) underwent VBG. Prospective follow-up data were collected to determine the success of the operative procedure in terms of weight loss, patient satisfaction, and lifestyle. Follow-up to date, death, or subsequent bariatric reoperation was 99% (72 of 73 patients). Two patients, however, declined research authorization, and their data were of necessity excluded. Patients were selected for weight reduction surgical procedures because of serious weight-related morbidity and underwent preoperative assessment by a multidisciplinary team including a psychologist, an endocrinologist, an internist, a dietitian, and a surgeon. All patients undergoing VBG, except two with weight-related morbidity, had a body mass index (BMI) ≥38 (BMI = [weight in kg] ÷ [height in meters]^2). Eighty-nine percent, however, had already developed concomitant, direct weight-related medical conditions including severe lower back or lower extremity large-joint degenerative arthropathy (63%; 16% were maintained on chronic anti-inflammatory drugs), hypertension (47%; 32% were on antihypertension medication), diabetes mellitus (31%; two patients were insulin dependent), asthma (9%; all were using regular bronchodilators), sleep apnea (14%), and venous insufficiency (11%). Most patients had a strong family history of severe weight-related comorbidity. No operations were performed for cosmetic reasons. In previous conservative attempts, all patients had failed long-term weight reduction; however, 58 (82%) of 71 had been able to lose weight (23 ± 2 kg) but were able to maintain the weight loss for only 1 to 24 months. A pamphlet detailing the different operative procedures and a separate pamphlet addressing the postoperative dietary protocol were given to all patients before operation.

Operative Procedure

We performed a modification of the VBG described by Mason[10] (Fig. 1). The vertical staple line was applied initially by using a Surgeons Choice P1 double 90 linear stapler (3M Company, St. Paul, Minn.) and later by using an Autosuture TA90B linear stapler (U.S. Surgical Corp., Norwalk, Conn.). These staplers inserted two rows of staples simultaneously. A small proximal gastric pouch (approximately 15 to 20 ml) was made by snuggling the linear stapler against a 32 F orogastric tube positioned along the lesser curvature of the stomach; no attempt was made to quantify objectively the volume of the proximal pouch as described by Mason[10]; however, the pouch

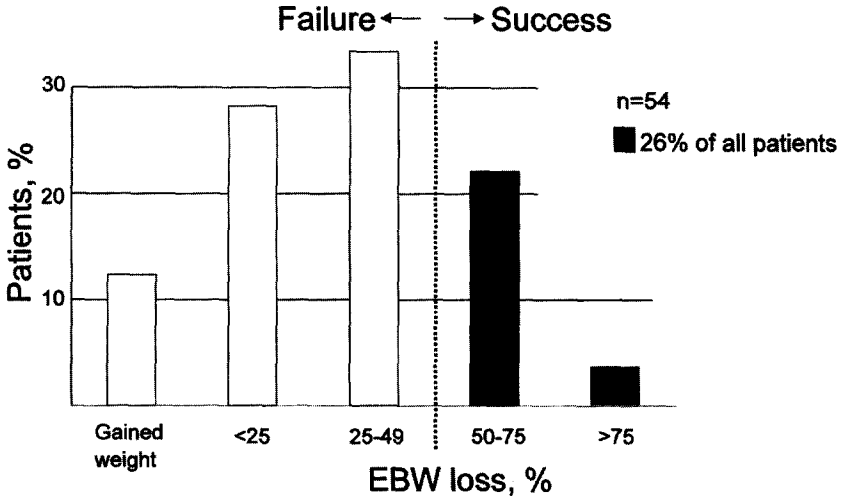

Fig. 1. Weight loss after VBG, expressed as percentage of EBW lost, in the 54 patients with more than 10 years' follow-up and a persistent VBG anatomy. We considered weight loss of ≥50% EBW as a successful result.

was made as small as possible with the rostral part of the linear staple line at the left gastroesophageal junction (angle of His). The stoma on the lesser curvature was externally banded using polypropylene mesh with an external circumference between 4.5 and 5 cm; a "tighter" external band (circumference of 4.5 to 4.7 cm) was generally used in the heavier patients (weight more than 130 kg). Perioperatively patients were given intravenous prophylactic antibiotics (cefazolin), "minidoses" of heparin (5000 U subcutaneously every 8 or 12 hours), and applications of sequential graded-compression leg wraps (SCD, Kendall Healthcare Products Co., Mansfield, Mass.). Concomitant cholecystectomy, performed in 47% of the patients, was usually undertaken routinely either for palpable gallstones or to prevent the future development of gallstones and their sequelae with postoperative weight loss.[14] Additional concomitant procedures included umbilical herniorrhaphy (16%) and ventral herniorrhaphy (4%). Nasogastric tubes were positioned intraoperatively with aspiration ports above and below the banded stoma and then removed a few days postoperatively.

Patients underwent intense counseling by our hospital dietitians and began a strict dietary protocol postoperatively. Progressive 24-hour trials were initiated of 30 ml/hr of clear liquids, 60 ml/hr of clear liquids, 60 ml/hr of full liquids (milk-based products, low-residue cereals), and finally pureed foods (2 ounces three times a day). Patients were then dismissed from the hospital with instructions to eat 2 ounces of pureed foods three times a day, and they were encouraged to sip low-calorie liquids between meals. Our dietary pamphlet explained in great detail the recommended dietary progression.

Six weeks postoperatively, the diet was gradually advanced to regular food as tolerated during the next 2 to 4 months. Patients were instructed in defined eating habits such as stopping further oral intake when a feeling of being "full" was noted, chewing food extremely well, extending each meal over a 45-minute period, and avoiding high-calorie liquids and especially ice cream.

Follow-Up

A surgeon assessed patients 6 weeks postoperatively and again at 3 months in conjunction with an internist and a dietitian specializing in obesity therapy. Medical and dietary follow-up was conducted at the Mayo Clinic with regional patients and, whenever possible, with nonlocal patients. Follow-up data were collected prospectively. Standardized questionnaires were mailed to all patients 3, 6, 12, 18, 24, 36, and 48 months postoperatively. In addition, we contacted all patients 10 and more years after the operation. Patients who failed to return their questionnaires were contacted either by a repeat mailing of another questionnaire or, when necessary, by direct telephone interview. Despite our attempts, complete early follow-up data at 1, 2, 3, and 4 years were available only in 96% (57 of 70), 86% (52 of 70), 81% (44 of 70), and 66% (34 of 70) of patients, respectively, even with repeated efforts at patient contact by us. These percentages are higher than those of many other weight maintenance studies,[15,16] but we acknowledge that a more complete response would have been ideal. In particular and most important, our 10-year follow-up was complete in all but one (72 of 73) of the patients. During these 10 and more years, 14 patients have undergone reoperation (12 before the 10-year follow-up). Six patients died, four of whom had a follow-up of less than 10 years. As stated earlier, two patients have refused research authorization. After subtracting the 12 patients who were reoperated, the four with less than 10-year follow-up who died, the two who denied research authorization, and the one patient who was lost to follow-up, we concentrated on analyzing data from the 54 patients with a VBG anatomy who had actual weight data 10 and more years after VBG; we also analyzed the 12 patients who were reoperated.

Weight Loss Data

We quantitated weight in kilograms, EBW (in kg), BMI, and percentage of EBW. Ideal body weight was calculated from the standard weight data tabulated by the Metropolitan Life Insurance Company. Weight loss is expressed as kilograms of weight lost, percentage of EBW lost, and most important as percentage of patients who lost 50% or more of their EBW. In this 10-year follow-up, we considered VBG to be a successful operation for patients who did not require a direct VBG-related reoperation or who achieved and maintained greater than 50% loss of their initial EBW.

Statistical Analysis

The distributions of actual weight values (in kg), BMI, and EBW and weight loss at 10 years postoperatively for kilograms lost and loss of percentage EBW were summarized as mean ± standard error of the mean (SEM) separately for the entire cohort (n = 70) and specifically for those patients (n = 54) who maintained a VBG anatomy 10 or more years after VBG (Table I).

Table I. Weight data in patients followed prospectively after VBG

	Before VBG	After ≥10 yr
All patients (n = 70)*		
Absolute weights		
Weight (kg)	138 ± 3	108 ± 2
EBW (kg)	75 ± 3	45 ± 3
BMI (kg/m²)	49 ± 1	39 ± 1
% EBW	120 ± 5	73 ± 5
Weight loss data		
Kg lost	—	28 ± 4
% EBW loss	—	37 ± 5
% Patients who lost >50% EBW	—	36
Patients with VBG anatomy (n = 54)†		
Absolute weights		
Weight (kg)	138 ± 4	114 ± 3
EBW (kg)	75 ± 3	51 ± 3
BMI	49 ± 1	41 ± 1
% EBW	119 ± 5	82 ± 5
Weight loss data		
Kg lost	—	24 ± 3
% EBW loss	—	30 ± 4
% Patients who lost ≥50% EBW	—	26

VBG = vertical banded gastroplasty; EBW = excess body weight; BMI = body mass index.
*Includes all 70 patients, 12 of whom were reoperated, and includes their follow-up data *after* reoperation and four others at the time of their death before the 10-year follow-up.
†Excluding 12 patients who were reoperated and four who died without 10-year follow-up.

RESULTS

Operative Mortality and Morbidity

There were no in-hospital deaths. Surgical morbidity included wound infection in six patients (9%) and an intra-abdominal abscess and pulmonary embolus in one patient each. One patient had prolonged fever and one had intra-abdominal bleeding requiring 4 units of blood. No reoperations were required. The mean duration of hospitalization was 8 days with a range of 6 to 29 days.

Long-Term Mortality and Morbidity

Six patients died during the follow-up of more than 10 years. One patient died 18 months postoperatively of a pulmonary embolus. One each died of alcohol-induced liver failure, cardiac disease, and "natural causes" (age 78 years) at 9, 9, and 10 years after operation, respectively. Two other patients died 12 years postoperatively because of ischemic heart disease. Fourteen patients (20%) were reoperated, including 12 at 3.5 ± 0.1 years after VBG and two others at 10 and 12 years, respectively, after VBG. Reoperation was undertaken in 13 because of poor weight loss (mean BMI 44 ± 1 at the time of reoperation), only two of whom had staple line disruption. Additional reasons for reoperation were frequent vomiting in four patients and symptoms of severe gastroesophageal reflux disease (GERD) in five, one of whom had an anatomically intact VBG and had experienced a 60% EBW loss after 3 years, but had such severe medically nonresponsive GERD that conversion to Roux-en-Y gastric bypass was necessary to treat the GERD. Other long-term morbidity included ventral (incisional) hernias in 16 (23%) of 71 patients, four of whom have undergone operative repair. Stomal stenosis was dilated in four patients with relief of symptoms.

Weight Loss

Most of the absolute weight loss occurred within the first 18 postoperative months with an EBW loss of 51 ± 3% to a BMI of 36 ± 1. Weight increased continually after that. The overall group of patients had a median BMI of 39 ± 1 (40 ± 3% EBW loss) at 4 years (n = 32) and 39 ± 1 (37 ± 5% EBW loss) at 10 years (n = 70) compared to an initial BMI of 49 ± 1 (see Table I).

Table II. Patient satisfaction in group of patients alive who were not reoperated and maintained a VBG anatomy

	1.5 yr (%) (n = 39)	3 yr (%) (n = 37)	10 yr (%) (n = 54)
Overall satisfied and/or improved vs. before VBG	92	78	48
Early postprandial satiety (yes)	85	68	57
Diet (regular food)	100	97	98
Appetite			
Decreased	74	70	47*
Increased	5	8	16*
Unchanged	21	22	37*
Food not tolerated			
Steak	68	69	63*
Pork	49	47	33*
Turkey	36	28	33*
Hamburger	36	39	32*
Bread	49	33	25*
Fruit	18	0	3*

*n = 32.

One patient was reoperated 2.3 years postoperatively because the stoma was believed to be too wide; the stoma was narrowed to a 4.5 cm banding but no further weight loss occurred (EBW loss 4 years later was only 21%). The other 11 patients who were reoperated within the first 10 years after VBG were converted to either a Roux-en-Y gastric bypass (n = 9) or a partial biliopancreatic bypass (n = 2). The EBW loss prior to reoperation was only 28 ± 1% (mean of 3.6 ± 0.1 years after VBG) but increased to 76 ± 2% at 8 ± 1 years after reoperation; BMI at latest follow-up was 31 ± 1.

When evaluated critically against our goal of losing at least 50% of EBW, only 50% and 40% attained this goal at 1.5 and 3 years postoperatively, respectively. Of the 54 patients who had follow-up of more than 10 years with no reoperation (maintenance of VBG anatomy), only 14 (26%) had maintained an EBW loss of more than 50%. In Fig. 1, the distribution of percentages of EBW loss is shown. If we define failure as the need for reoperation for VBG-related complications or the inability to maintain an EBW loss of ≥50% at 10 years postoperatively, then the overall failure rate was 79% (52 of 66).

Subjective Patient Satisfaction

A qualitative evaluation of outcome is summarized in Table II. Overall, at 3 years postoperatively, 93% considered themselves satisfied and improved. Early postprandial satiety was maintained in 68% of patients. Overall appetite was decreased in 74% at 1.5 years postoperatively and in 28% at 10 years postoperatively. All but one patient was able to eat regular food. The most common foods that were not well tolerated by patients included steak (41%), pork or hamburger (20%), and bread (9%). Concerning adverse gastrointestinal symptoms after 10 years, symptomatic heartburn and vomiting occurring more than one time per week persisted in 16% and 22%, respectively.

DISCUSSION

Our long-term 10-year follow-up of 70 patients followed prospectively showed that results after VBG were unsatisfactory and that VBG is not a durable, effective bariatric procedure in the majority of patients with morbid obesity in our practice. Twelve patients (18%) underwent reoperation within the 10-year follow-up (11 for unsatisfactory weight loss) and an additional 40 patients (61%) failed to maintain an EBW loss of more than 50%, leading to an overall failure rate of 79% at 10 years after VBG. These results, although probably marginally better than the results expected with a nonoperative medical dietary approach,[17,18] are clearly unsatisfactory, especially because a maladaptive eating behavior persists in more than 20% of the patients with a maintained VBG anatomy.

VBG and RYGB are the two bariatric operations currently "sanctioned" by the 1991 NIH Consensus Conference.[9] VBG was designed by Mason[10] more than 20 years ago. This operation is attractive in theory; it was designed and adopted because it is technically easy, does not require creation of a formal anastomoses, and involves no partial or total bypass of any gastrointestinal segment. Although some centers have reported good results in weight loss,[19,20] most others have not been able to reproduce such good results.[21-24] Our initial report of this patient group[13] followed up

to 3 years postoperatively was disappointing as well. Our current long-term follow-up confirms our previous early results of unsatisfactory weight control by VBG at 3 years[13] and shows that results continue to deteriorate over the ensuing 7 years. Moreover, the anatomy of VBG appears to predispose patients to symptoms of GERD,[25] staple line disruption,[23] mechanical or functional stomal obstruction,[26] and a maladaptive eating behavior that make VBG unattractive as an effective bariatric procedure.

Weight loss, in our experience, was clearly unsatisfactory after VBG. By 10 years postoperatively, 40 (61%) of the 66 available patients had failed to maintain at least a 50% EBW loss and 11 additional patients (17%) had undergone reoperation because of inadequate weight loss or failure to reverse the weight-related comorbidity. Interestingly only 2 of the 11 reoperated patients had an objectively documented staple line dehiscence; the remainder had an intact VBG anatomy. Contrast this with our current experience[4] with primary vertical disconnected Roux-en-Y gastric bypass; at 4-year follow-up more than 70% have maintained greater than 50% EBW loss with a concomitant decrease in weight-related comorbidity. In addition, subjective patient satisfaction after 3 years was high (93%), and only 2% of patients had any problems with vomiting or intolerance of solid foods including red meats.

The VBG anatomy also predisposes patients to several complications that we and others have noted. The narrow (<1.5 cm) stoma of the VBG was designed to slow gastric emptying from the proximal pouch and to obligate patients to chew their food *very* thoroughly (in itself a form of behavior modification). The small-volume proximal pouch and the narrow stoma should limit the amount of food ingested in any one meal and induce a rapid feeling of satiety. However, this anatomy also predisposes patients to vomiting; at 3-year follow-up, 60% of patients were unable to tolerate steak, hamburger, turkey, and untoasted bread. Although many were no longer vomiting, these latter patients had learned to avoid vomiting by changing their diet to nonbulky, low-fiber foods, and unfortunately often to ice cream, milkshakes, and other liquid meals, often of high caloric density. With this change in diet, gastric emptying appeared to be faster (although we have no objective data to prove this hypothesis), and the amount of these high-calorie liquid foods able to be ingested also increased. Surprisingly, even though the diameter of the anastomosis we use for Roux-en-Y gastric bypass is only 7 mm,[27] vomiting is unusual, and almost all foods are readily tolerated by more than 80% of patients. The problems with the VBG anatomy may be related to the length (as well as the width) of the VBG stoma (~1.5 cm). These problems after VBG have been termed maladaptive eating disorders, which cause a switch to less healthy foods and frequent vomiting—a syndrome almost nonexistent after Roux-en-Y bypass.

Another problem we have noted is the development of GERD symptoms after VBG. Although GERD is common in the obese patient (~16%), at 3 years after VBG, GERD symptoms were present in 38%. During the 10-year follow-up, five patients underwent reoperation, at least in part, for GERD symptoms and without stomal stenosis. We have previously reported our experience with conversion from VBG to Roux-en-Y gastric bypass in 25 patients.[25] Some of these latter patients developed a stenosis at the banded stoma, because of either external compression, band erosion, or "tilting" of the band or ring, all of which effectively reduce the functional diameter of the stoma channel. Among our 70 patients, four required endoscopic balloon dilatation of the stoma with good results. None of our patients, to our knowledge, have developed band erosion, but this is a well-recognized complication.[26,28,29]

We hope that the lessons learned in the past decades in patients with solely restrictive procedures will be applied in the future. Specifically, we remain somewhat skeptical about the laparoscopically placed adjustable gastric band, the newest bariatric procedure used widely in Europe. This procedure is again purely restrictive. Initial results were disappointing because of technical problems or defects.[30-33] Some reports actually mention complications comparable to those of VBG such as esophagitis, vomiting, and heartburn,[34] and others see the same type of weight loss followed by weight gain as after VBG,[35] which as shown by us is not favorable in the long run. Other results, however, appear quite encouraging.[36,37] The real question of whether a change of diet to high-caloric-density liquids or semisolids, as described by Brolin et al.,[38] will negate the initial benefits of the minimal access procedure to insert the band remains unanswered. The success of gastric banding requires long-term follow-up of these series.

In summary, VBG failed to effectively control weight in 79% of the patients and induced in every fifth patient persistent—at least weekly—vomiting. If the laparoscopic equivalent of this procedure (laparoscopic banding) will produce better long-term results due to the lack of a staple line (that can disrupt) and adjustability of the stoma is questionable. In our view, RYGB has proved effective in reducing comorbidity in patients with morbid obesity by obtaining a durable weight loss in more than 70% of these patients when they are evaluated 4 years postoperatively.[4] We are concerned that exclusively restrictive procedures will be ineffective in the long term and will not provide a

good quality of life with satisfactory weight loss and the concomitant improvement in weight-related morbidity for the majority of our patients. For this reason, we currently advocate vertical disconnected RYGB as our procedure of choice in patients with morbid obesity. Currently, prospective randomized studies are underway in the United States to evaluate the effectiveness of adjustable laparoscopic banding. We will continue to carefully evaluate the results of a minimal access approach to gastric bypass.[39,40]

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Discussion

Dr. Harvey J. Sugerman (Richmond, Va.). It is nice to see a long-term study on VBG; very little long-term data are available on this operation from anywhere. Dr. Balsiger's data confirm the results of our earlier randomized study comparing VBG to gastric bypass. One of the problems we noted in the patients who failed VBG was that many did not correct their comorbidity or their comorbidity would return with regaining of lost weight. There are some who think, like Dr. George Blackburn, that the loss of 10% of weight—or 40% of excess weight—should be sufficient, and Dr. Mason who looked at failure as the loss of less than 20% of excess weight. Have you looked at other comorbid conditions besides GERD in this patient population, such as sleep apnea, hypoventilation, hypertension, diabetes, and so forth, to see how many of these patients have failed to correct their obesity comorbidity with this operation?

One of the nice things about VBG is that it is relatively easy to convert to gastric bypass. How have your patients done with conversion to gastric bypass?

Dr. B. Balsiger. I think the question about comorbidity is really an important one. Unfortunately, our study design does not allow us to make statements about that. This is one of the limitations of the study. This is a patient-reported data study. We sent out questionnaires and we conducted phone interviews, so we cannot really answer that question from our study. Dr. Brolin showed, although in a study Roux-en-Y gastric bypass, that resolution of hypertension is clearly dependent on the BMI reduction. In regard to your second question, our patients did very well after the conversion. They started out, as you saw, with a preoperative BMI of 44 and after a follow-up of 8 years, the BMI was reduced to 30.

Dr. Bruce D. Schirmer (Charlottesville, Va.). I was surprised to see that you had no band stenosis or reoperation for stenosis at the band site. I was curious about that because we have seen that in our experience of long-term follow-up in these patients. Also, how did you construct the vertical band itself? Was it divided or not? In the beginning, we did not divide our bands, and we saw a significant incidence of staple breakdown. Did you?

Dr. Balsiger. We did not need to reoperate because of stenosis, but four of our patients had stenosis that required endoscopic dilation; these patients did very well after two to six dilations. Our staple line was not divided and we did not routinely perform endoscopic examination of our patients to determine whether they had a staple line disruption. However, of the 11 patients who were reoperated because of poor weight loss, only two had a breakdown of the staple line.

Dr. Robert Brolin (New Brunswick, N.J.). I think that your experience is very representative of the nationwide experience with gastroplasty. Have you looked at eating behavior? We and Dr. Sugerman have shown that these patients tend to become sweet eaters, milk shake drinkers, and ice cream eaters.

Dr. Balsiger. We did not look at the calorie intake or sweet-eating patterns of our patients. However, we noted whether patients tolerated steak or bread and food of that sort. After 10 years, 63% of the patients did not tolerate steak and 30% of the patients did not tolerate hamburger or turkey or pork. An additional 25% did not tolerate bread.

Comparison of Ceftibuten vs. Amoxicillin/Clavulanic Acid as Antibiotic Prophylaxis in Cholecystectomy and/or Biliary Tract Surgery

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A randomized, comparative, prospective clinical trial was carried out at a tertiary care center to compare the efficacy of two antibiotic regimens in the prophylaxis of postoperative infection in patients undergoing biliary tract surgery. One hundred patients undergoing cholecystectomy or biliary tract exploration were randomly allocated to one of the following antibiotic regimens: the standard regimen of three doses of amoxicillin/clavulanic acid (1000/200 mg) given by intravenous infusion, or a single dose of ceftibuten (400 mg) given orally. Patients were monitored during their stay in the hospital and over a 2 week period as outpatients. Fifty adult patients were included in each group. Mean age was 49 years, and sex distribution was 82 women and 18 men. The groups were comparable in terms of demographic characteristics and comorbidity. There were no cases of postoperative infection in the ceftibuten group, but five cases of infection occurred in the amoxicillin/clavulanic acid group ($P < 0.05$). No adverse effects were observed with either antibiotic. The treatment cost per patient was significantly lower for ceftibuten. The results indicate that ceftibuten is well tolerated and more effective than amoxicillin/clavulanic acid for prophylaxis following gallbladder and biliary tract surgery. In addition, ceftibuten has the advantage of being more cost-effective and easier to administer than amoxicillin/clavulanic acid so it could be considered as an alternative for antibiotic prophylaxis in these types of surgical procedures. (J GASTROINTEST SURG 2000;4:606-610.)

KEY WORDS: Ceftibuten, prophylaxis, biliary surgery, cephalosporins

The use of prophylactic antibiotics has significantly reduced the incidence of infection following surgical procedures of the biliary tract.[1,2] The regimens most often used include first- or second-generation cephalosporins, which are sometimes combined with aminoglycosides and/or clindamycin to broaden their antibacterial spectrum.

In an earlier study we compared the regimen used at our institution at that time (cephalothin + clindamycin) with a regimen of amoxicillin/clavulanic acid[3] and found that administration of the latter yielded better results. This observation led our institution to introduce amoxicillin/clavulanic acid as the current standard regimen for prophylaxis of this type. However, since amoxicillin/clavulanic acid requires intravenous administration, additional costs are incurred because of the equipment, materials, and qualified staff that are needed. Therefore alternatives such as orally administered antibiotics with demonstrated effectiveness against the most common microbes in the biliary tract would prove less expensive and facilitate patient handling.

Broad-spectrum cephalosporins such as ceftibuten, cefetamet, cefixime, and cefpodoxime are available in oral formulations and offer various advantages. These include single daily dosing, good gastric tolerance and absorption, and high bioavailability.[4-6]

Ceftibuten has been shown to be well tolerated when administered orally, and it also has an expanded spectrum and outstanding stability against beta-

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lactamases.[7-9] Ceftibuten is known to be absorbed in the stomach; it has a relatively long half-life for this class of drug (2 to 3 hours), with a plasma clearance of 40 to 75 ml/min and a renal clearance of 30 to 50 ml/min; up to 70% of the dose is excreted unchanged in urine. Ceftibuten penetration into tissues and inflammatory secretions has been found to be excellent.[4-10] This drug has also been shown to be the most potent oral cephalosporin against enterobacteria and staphylococci, but with little activity against *Pseudomonas* species.[11-15] The emergence of resistant strains is rare and, similar to other beta-lactamases, it has synergistic activity with aminoglycosides.[13]

The objective of this study was to compare the efficacy, tolerance, adverse effects, and cost-benefit ratio of orally administered ceftibuten with amoxicillin/clavulanic acid administered intravenously as antimicrobial prophylaxis for surgery of the gallbladder and the biliary tract.

PATIENTS AND METHODS

This was a randomized, controlled, prospective clinical trial involving a third independent observer. The study was performed at a tertiary care center in Mexico City, and was approved by the institutional review board. All of the patients who agreed to participate in the trial gave informed written consent.

Patients were randomly allocated in a 1:1 ratio to receive either ceftibuten (400 mg orally) 2 hours before surgery or amoxicillin/clavulanic acid (1000/200 mg intravenously), one dose during induction of anesthesia and two additional doses postoperatively, separated by an interval of 6 hours.

Medical histories were taken by H.M.-F, E.P., or J.A. Patients over 16 years of age who were candidates for elective gallbladder and/or biliary tract surgery were considered eligible for the study. Exclusion criteria were as follows: known hypersensitivity to any of the drugs used in the study, age less than 16 years, pregnancy, acute or chronic renal failure (creatinine clearance <10 ml/min), a life expectancy of less than 30 days, ongoing infection confirmed within the 7 days prior to surgery, suspected biliary tract infection, total neutrophil count of 1000/mm^3 or less, and immunosuppressive drug therapy. All patients were monitored twice during their stay in the hospital and once a week for a period of 2 weeks as outpatients.

Postoperative infection was defined as any infection detected during the 15 days after surgery. Surgical wound infection was defined by the presence of purulent secretion from the wound, independent of the causative organism. Intra-abdominal abscess was defined by the presence of accumulated fluid in the abdomen, positive ultrasound detection, positive CT scan, or outflow of purulent matter through drainage tubes. Bacteremia was defined by the isolation of microorganisms from blood cultures.[16]

Good clinical response was defined as the absence of any type of infection and poor clinical response was the appearance of any infection after the surgical procedure. When infection was suspected, two blood cultures and a urine culture were obtained, along with culture of the purulent secretion in cases of surgical wound infection. Additionally, chest x-ray films were obtained when pneumonia was suspected, and abdominal ultrasound or CT scans when an intra-abdominal abscess was suspected.

Adverse effects, as determined by analysis of both clinical and laboratory data, were assessed for each of the patients included in the study. Any evidence of discomfort or intolerance to either oral or intravenous medication was recorded.

Continuous variables, such as age and laboratory data, were compared between groups using Student's *t* test. Quantitative variables, as well as the incidence of infections and adverse effects, were compared by means of Fisher's exact test. A significance level was established at $P < 0.05$.[17]

RESULTS

Patients who were candidates for elective gallbladder and/or biliary tract surgery were entered into the study. One hundred patients were randomly allocated to treatment: 50 each to the ceftibuten and the amoxicillin/clavulanic acid groups. Nine patients in each treatment group were male and the mean age of the study population was 48.9 years. With regard to other demographic parameters, the two treatment groups were well matched (Table I). More than 60% of patients in each group had comorbidity. The most common comorbid conditions were arterial hypertension, obesity, diabetes mellitus, and rheumatoid arthritis.

Twelve patients in total failed to complete the study: eight in the ceftibuten group and four in the amoxicillin/clavulanic acid group. Reasons for discontinuing the study included cancellation of surgery because of a contraindication to anesthesia (after randomization and drug administration) (n = 3), preoperative diagnosis of gallbladder infection with consequent initiation of combined antimicrobial therapy such as ceftriaxone and clindamycin (n = 7), lost to follow-up (n = 1), and death (n = 1).

There was a significant difference in the clinical responses of the two treatment groups (Table II). Five patients in the amoxicillin/clavulanic acid group developed surgery-related infections, including three patients with wound infections and two patients with intra-abdominal abscesses. Three patients in the

Table I. Patient characteristics and laboratory data

	Ceftibuten group	Amoxicillin group	*P* value
No. of patients	50	50	NS
Sex (M/F)	9/41	9/41	NS
Age (yr)	50 ± 15.4	47.7 ± 15.9	NS
Range (yr)	30-70	28-71	NS
Age >60 yr	14	13	
Comorbidity	32	32	
Gout	2	0	
Arterial hypertension	7	8	
Seizures	1	0	
Obesity	8	6	
Diabetes mellitus	5	7	
Ischemic cardiopathy	1	6	
Parkinson's disease	1	0	
Cirrhosis of the liver	1	0	
Rheumatoid arthritis	3	1	
Graves' disease	0	1	
Laboratory data			
Hemoglobin (g/dl)	13.1 ± 1.3	13.9 ± 1.1	
Hematocrit (%)	39.0 ± 4.1	40.1 ± 4.0	NS
Total leukocytes (thousands/ml)	7.02 ± 1.71	6.90 ± 1.81	NS
Total lymphocytes (thousands/ml)	1.84 ± 0.53	1.81 ± 0.49	NS
Albumin (g/dl)	3.9 ± 0.51	3.9 ± 0.52	NS

NS = not significant.

Table II. Indications for surgery, type of surgery, and complications

	Ceftibuten group	Amoxicillin group	Total
Reason for surgery			
Calculous chronic cholecystitis	40	42	82
Biliary pancreatitis	6	5	11
Gallbladder hydrops	1	0	1
Choledocholithiasis	2	2	4
Biliary dyskinesia	1	0	1
Biliary tract injury	0	1	1
Type of surgery			
Laparoscopic cholecystectomy	31	32	63
Open cholecystectomy	13	12	25
Exploration of the biliary tract	3	4	7
Hepaticojejunostomy	0	1	1
Reconstruction of the biliary tract	0	1	1
Surgery canceled	3	0	3
Type of drain			
T-tube	3	2	5
Open	0	3	3
Complications	0	5 (10.1%)†	5 (5.5%)
Surgical wound infection	0	3 (6.5%)*	3 (3.3%)
Intra-abdominal abscess	0	2 (4.3%)*	2 (2.2%)
Death	1	0	1

*Only those patients who could be evaluated were taken into account: 43 in the ceftibuten group and 46 in the amoxicillin/clavulanic acid group.
†$P < 0.05$.

amoxicillin/clavulanic acid group had open drains, but none of them developed a postsurgical infection. No postsurgical infections were recorded in the ceftibuten group during the treatment and follow-up periods.

Among those in the amoxicillin/clavulanic acid group who had wound infections, amoxicillin/clavulanic acid–resistant *Escherichia coli* was isolated in one patient and oxacillin-resistant *Staphylococcus aureus* in another two. *E. coli* was isolated from intra-abdominal abscesses in two patients in the amoxicillin/clavulanic acid group; in one of these patients *Clostridium perfringens* was isolated as well, and in the other patient *Citrobacter freundii* and *Enterococcus faecium* were isolated. All of these patients progressed satisfactorily, with local debridement in the cases of wound infection, and percutaneous drainage in addition to parenteral ceftriaxone plus clindamycin, and ceftazidime plus amikacin plus clindamycin, respectively, for the two patients with intra-abdominal abscesses.

Other recorded postsurgical events were a seroma in the umbilical surgical wound of one patient (ceftibuten group) who had undergone laparoscopic cholecystectomy, and perforated acute appendicitis with secondary abdominal sepsis in one patient (amoxicillin/clavulanic acid group) 1 week after laparoscopic cholecystectomy. One 65-year-old man in the ceftibuten group, who had a history of diabetes mellitus, ischemic cardiomyopathy, and hypercholesterolemia, died as a result of cardiogenic shock after a myocardial infarction (ceftibuten group). This occurred 1 week after he had undergone a cholecystectomy and surgical exploration of the biliary tract. There was no evidence of infection at the time of death.

No antibiotic-related adverse effects were observed in either of the two treatment groups, and no cases of drug intolerance were recorded.

An analysis of the costs of both treatment regimens revealed that the total cost of ceftibuten prophylaxis per patient was $8.72, whereas the cost of amoxicillin/clavulanic acid was $41.56. The cost of intravenous amoxicillin/clavulanic acid prophylaxis included the cost of the microdrip drug delivery apparatus in addition to the drug itself.

DISCUSSION

The value of antimicrobial prophylaxis has previously been established, as evidenced by the decrease in infectious complications in almost all cases of clean-contaminated surgery including surgery of the gallbladder and the biliary tract.[18-21] In addition to the efficacy of oral antibiotics in colorectal surgery,[22] experience with these antibiotics in this context is limited to a few reports on their efficacy in orthopedic,[23] gastroduodenal,[24] vascular,[25] and urologic[23] surgery. There appear to be no previous studies on oral antibiotic prophylaxis for surgery of the biliary tract. In this study, a statistically significant difference in clinical responses was determined in favor of the single-dose oral ceftibuten regimen when compared to intravenous infusion of three doses of amoxicillin/clavulanic acid. Moreover, oral ceftibuten offers a distinct advantage in terms of cost over an amoxicillin/clavulanic acid regimen.

In this study, no infectious complications were observed in the ceftibuten group. These findings compare favorably with the results of a previous investigation at our institution, in which cephalothin plus clindamycin was compared to a regimen of amoxicillin/clavulanic acid for antimicrobial prophylaxis in surgery of the biliary tract.[3] Six of 22 patients developed wound infections, and one of them had bacteremia (during prophylaxis with cephalothin and clindamycin), in contrast to none of the 22 patients who received prophylaxis with amoxicillin/clavulanic acid. The widespread use of amoxicillin/clavulanic acid for other types of infections could explain the appearance of bacteria that are resistant to this antibiotic and a decrease in its effectiveness as a prophylactic drug. In other studies of orally administered antimicrobial prophylaxis for surgical procedures, there is a marked predominance of the use of quinolones over cephalosporins.[24-26]

In the present study, most patients (64% of each group) had comorbidity. At our institution we concentrate on higher risk patients and this could be the reason for the higher rate of infectious complications noted in the amoxicillin/clavulanic acid group (10.1%) as compared with other surgical series in lower risk patients.[18-20]

Ceftibuten satisfies several criteria, which emphasizes its utility for surgical prophylaxis: it is well tolerated, it is readily absorbed by the stomach, it is easy to administer, and it is inexpensive. The broad-spectrum coverage afforded by ceftibuten also eliminates the need for combination therapy, thus avoiding the potential risk of toxicity. Only a single dose of ceftibuten is required in the preoperative period, since its long half-life in the bloodstream helps to ensure safe serum and tissue concentrations. Furthermore, the cost inherent in the administration of drugs via the parenteral route may be avoided.

CONCLUSION

The results of this study indicate that a single dose of ceftibuten appears to be a useful regimen for prophylaxis in surgery of the gallbladder and biliary tract,

and is more effective than three doses of amoxicillin/clavulanic acid. The potential superiority of the regimen is suggested by the absence of organisms resistant to this antibiotic, in contrast to the appearance of enterobacteria resistant to amoxicillin/clavulanic acid. Moreover, its ease of administration and lower cost make it even more attractive as a prophylactic antibiotic.

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Hemangioma of the Spleen: Presentation, Diagnosis, and Management

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Splenic hemangioma is a rare disorder but remains the most common benign neoplasm of the spleen. It often has a latent clinical picture; however, spontaneous rupture has been reported to occur in as many as 25% of this patient population.[1] Treatment most often consists of splenectomy. This report reviews an 8-year experience with splenic hemangioma at Mayo Clinic. Thirty-two patients were identified with SH during the 8-year study period. The average age was 63 years (range 23 to 94 years) with 17 women and 15 men. Six patients presented with symptoms potentially related to the SH. The remainder (80%) were asymptomatic, and the SH was discovered incidentally during evaluation for other disorders. A mass or palpable spleen was appreciated in only four patients (12.5%). SHs ranged in size from 0.3 to 7 cm maximum diameter. A diagnosis of SH was made in 11 patients based on the findings of a splenic mass on computed tomography or ultrasound. Each of these SHs was ≤4 cm. Three of the 11 patients had multiple SHs. All 11 patients were managed successfully with observation. All but one of the patients remains asymptomatic, and no complications have developed during follow-up (range 0.6 to 7 years, mean 2.9 years). The diagnosis of splenic hemangioma was made at the time of surgery in the remaining 21 patients (65%). Splenectomy was performed for suspicion of primary or secondary splenic pathology. There were no instances of spontaneous rupture of the SH. Small splenic lesions, which meet the radiologic criteria for hemangiomas, may be safely observed. (J GASTROINTEST SURG 2000;4:611-613.)

KEY WORDS: Spleen, hemangioma, angiosarcoma

Although hemangiomas represent the most common primary neoplasm of the spleen, they remain rare disorders. Hodge[1] reported the first case of a splenic hemangioma (SH) treated successfully by surgical extirpation in 1895. Less than 100 patients have been reported in the medical literature.[2] The clinical presentation is often latent with many diagnoses made only at autopsy.[3] Several previous reports[4-10] have discussed clinical presentation, radiologic appearance, histology, and potential complications, but the indications for surgical intervention remain unclear. Our aim is to review our experience with SH at a large tertiary referral center, and to develop and evaluate treatment guidelines.

MATERIAL AND METHODS

The computerized patient database of the Mayo Clinic, which includes surgical and pathology records, was searched for patients diagnosed with SH between 1990 and 1998. The medical records of these patients were analyzed for patient demographics, clinical presentation, diagnostic evaluation, surgical indications, and follow-up. Patients not undergoing splenectomy were contacted by questionnaire to assess their current status. Follow-up was 100% complete, and all patients have been contacted within the past six months.

RESULTS

Thirty-two patients were identified with SH during the 8-year study period. Their average age was 63 years (range 23 to 94 years), with 17 women and 15 men. Six patients (19%) presented with symptoms (pain and/or left upper quadrant fullness), and four patients (12.5%) presented with palpable masses of varying sizes (Table I). All 10 of these patients underwent splenectomy and had uneventful postoperative

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Table I. Clinical presentation and treatment of 21 surgical patients with splenic hemangiomas

Signs/symptoms	Maximum diameter (cm)	Therapy	Complications
Pain	7	Splenectomy	None
LUQ fullness	7	Splenectomy	None
LUQ fullness	2.5 (multiple)	Splenectomy	None
Pain	6	Splenectomy	None
Pain/splenomegaly*	6	Splenectomy	None
LUQ fullness	Infiltrated	Splenectomy	None
Palpable spleen	0.4	Splenectomy	None
Palpable spleen	7	Splenectomy	None
Palpable spleen	0.9	Splenectomy	None
None	2	Splenectomy	None
None	1.5 (two)	Splenectomy	None
None	1.5 (multiple)	Splenectomy	None
None	1	Splenectomy	None
None	1	Splenectomy	None
None	1.5	Splenectomy	None
None	3.5	Splenectomy	None
None	1	Splenectomy	None
None	1	Splenectomy	None
None	1	Splenectomy	None
None	1 (multiple)	Splenectomy	None
None	3.5 (multiple)	Splenectomy	None

LUQ = left upper quadrant.
*This patient presented with pain and palpable spleen.

courses. The remainder of the patients (81%) were asymptomatic, and the SH was discovered incidentally during evaluation for other disorders. A diagnosis of SH was made in 11 patients based on the findings of a splenic mass on computed tomography (CT) or ultrasound. Nine lesions were discovered by CT. In each of these nine patients, the SH was ≤4 cm and showed early vascular enhancement, and three of the nine patients had multiple SHs. Two lesions were discovered by ultrasound. All 11 patients have been managed successfully with observation only. All but one of these patients remains asymptomatic, and no complications have developed during follow-up (range 0.6 to 7 years, mean 2.9 years). One patient has persistent but nonspecific abdominal pain. Unfortunately, results of subsequent radiologic examinations are not available. Treatment of SH was determined by the physicians caring for the patient.

The diagnosis of SH was made at the time of splenectomy in 21 patients. Twenty of these patients had a CT scan that did not identify a splenic mass. Splenectomy was performed for several reasons including suspicion of primary splenic pathology (14 patients), concern about metastatic disease with a known nonsplenic neoplasm (4 patients), or staging laparotomy for Hodgkin's lymphoma or a lymphoproliferative disorder (3 patients). There were no instances of spontaneous rupture of the SH.

SHs ranged in size from 0.3 to 7 cm maximum diameter. Nineteen patients presented with a single lesion (14 were ≤2 cm). Five patients (15%) had a single SH ≥4 cm. Thirteen patients had multiple SHs (8 were <2 cm). Eight of the 13 patients with multiple SHs had three or more individual SHs, whereas three patients had innumerable small SHs involving most of the spleen. Two patients had two lesions each.

DISCUSSION

Hemangiomas of the spleen represent the most common benign neoplasm of the spleen. The incidence varies from 0.03% to as high as 14% in an autopsy series.[2] Clinical recognition occurs most commonly in middle-aged adults.[2] Many serious disorders become evident only in middle life and, in our experience, SH is usually found incidentally during evaluation of other disorders. Our experience and that of others[2,3] suggests that the majority of patients with SH (especially with lesions <4 cm) are asymptomatic. Larger SHs may be more prone to rupture than smaller ones,[2] although this observation may be anecdotal. Six of our 32 patients presented with symptoms potentially related to SH. The SHs in these six were all ≤6 cm. It is questionable whether the SH directly caused the left upper quadrant pain or fullness in these six patients. None of the SHs had ruptured.

Prior to the advent of objective imaging tests, such as CT, ultrasonography, and, most recently, magnetic resonance imaging, SHs were rarely diagnosed (or suspected) preoperatively. More recently, SHs are being recognized with increasing frequency preoperatively, similar to hepatic hemangiomas.[11] SHs appear on CT scans as single or multiple lesions that are usually homogeneous, hypodense, or multicystic. They may contain calcifications and generally demonstrate peripheral enhancement after intravenous contrast injection.[8] Ultrasound often demonstrates round, echogenic masses, with or without cystic areas.[9] Confident preoperative recognition and differentiation of SH from other lesions still remains difficult.[3,4] Of the 29 patients who had a preoperative CT in our series, the diagnosis of SH was made confidently in nine patients. In many of the other patients, especially those with the small (<2 cm) hemangiomas, the SHs were not recognized on scans. The SHs were only discovered intraoperatively as palpable masses or histologically by the pathologist. The spleen was removed for suspicion of primary splenic pathology, concern about metastatic disease with a known nonsplenic neoplasm, and staging for Hodgkin's lymphoma or a lymphoproliferative disorder.

The potential for malignant transformation of SH to angiosarcoma is unknown. Malignant transformation is stated to occur more frequently with a large SH or when the spleen is diffusely involved with multiple SHs.[1,2,12] However, specifics regarding the potential of malignant degeneration are unknown. Wick et al.[13] reviewed a 51-year experience at the Mayo Clinic with malignant neoplasms of the spleen, and only six angiosarcomas of the spleen were noted. Most patients with SH are asymptomatic and the possibility of malignant transformation appears remote at best.

Early reports suggested that SH presents with symptoms or spontaneous rupture.[2] Splenectomy was recommended for all cases of SH.[2] In contrast, we observed no patients who had spontaneous rupture. This may be explained by the prevalence of small SHs in our series and the absence of very large hemangiomas. Follow-up of 11 patients managed with observation confirms the benign course of small SHs.

The lack of direct complications related to small SHs in our series calls into question the recommendation that all SHs be treated by splenectomy. We recommend observation of patients with small, asymptomatic splenic lesions, which meet the radiologic criteria for hemangiomas. The approach is similar to the suggested management of hepatic hemangiomas.[4] Serial scanning would seem prudent until the SH is determined to be of stable size.

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Matrix Metalloproteinase Inhibition Improves Survival in an Orthotopic Model of Human Pancreatic Cancer

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Matrix metalloproteinases (MMPs) have been implicated in the growth and invasiveness of primary and metastatic tumors. Hypothesizing that MMP inhibition would slow cancer growth, the MMP inhibitor BB-94 (batimistat) was evaluated in an orthotopic animal model of human pancreatic carcinoma. Ten million human pancreatic cancer cells were surgically implanted into the pancreata of 30 athymic *nu/nu* mice. Intraperitoneal administration of 30 mg/kg BB-94 or vehicle control began 7 days after tumor implantation (13 mice with confirmed implantations in each group) and continued daily for 21 days, and then three times weekly until death or sacrifice at day 70. Representative tumors harvested from mice in each group were analyzed for presence and activity of MMP-2 and MMP-9. Animal weights were significantly higher in the BB-94–treated group at sacrifice (mean 58.4 ± 7.9 g vs. 39.8 ± 6.2 g; $P < 0.05$, Student's t test). The likelihood of survival to 70 days was significantly higher in the treated group (4 of 13 vs. 0 of 13, $P < 0.05$, Z-test for end points) than in the control group as was overall survival ($P = 0.03$, Wilcoxon test). Nine mice in the control group developed metastases to the liver, peritoneum, abdominal wall, or local lymph nodes, whereas only two mice in the BB-94 group had evidence of metastatic disease ($P < 0.02$, Fisher's exact test), in both instances confined to the abdominal wall. Tumors from treated mice manifested lower MMP activity than those from control animals. These reports support the use of MMP inhibitors alone or as an adjunct in the treatment of pancreatic cancer. (J GASTROINTEST SURG 2000;4:614-619.)

KEY WORDS: Pancreatic cancer, BB-94, matrix metalloproteinase, nude mouse, gel zymography

Despite significant reductions in the therapeutic complications associated with pancreatic cancer, local-regional invasion and metastases continue to thwart the efforts of both surgeons and oncologists in their attempts to achieve significant survival benefits in large numbers of patients.[1,2] The indolent onset and rapid progression of this disease precludes surgical therapy in most patients who are ultimately diagnosed, and these same characteristics exacerbate the already dismal prognosis in patients who are nonsurgical candidates.

With these characteristics in mind, recent attention has focused on the mechanism through which aggressive cancers, particularly pancreatic cancer, violate anatomic barriers and achieve local and distant foci of disease. Matrix metalloproteinases (MMPs) are a family of naturally occurring degradative enzymes thought to be primarily responsible for tumor progression through breakdown of the extracellular matrix and basement membrane.[3-6] The critical role that MMPs play in tumor growth and invasion became evident when high levels were documented in human colon cancer[7,8] and a host of other malignancies commonly arising in human subjects.[9-11] The introduction of a synthetic inhibitor of these enzymes has lead to subsequent animal trials designed to measure the in vivo effects of MMP inhibition. These studies have demonstrated not only a dramatic effect on survival

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but also a significant attenuation in the metastatic behavior of different cancers.[12-14]

Although this type of therapy has never been applied in the setting of pancreatic cancer, orthotopic animal models of human pancreatic cancer are well established and have been used to test other therapies.[15-19] MMP inhibition seems especially applicable in the setting of pancreatic cancer, given the high inherent proteolytic activity of the pancreas and aggressive behavior of cancers arising from it. We have applied such therapy in a model that mimics its potential use as an adjuvant to surgical therapy.[20] In the current study we sought to answer that question which applies to the majority of patients suffering from this illness, patients in whom surgical therapy is not indicated. Herein we initiated treatment with BB-94 in nude mice with established orthotopic pancreatic tumors to determine its effect on survival, metastases, tumor burden, and MMP activity.

METHODS

Preparation of Pancreatic Cancer Cell Line

Human pancreatic cancer (HPAC; American Type Culture Collection CRL-2119), a moderately differentiated pancreatic adenocarcinoma of ductal origin,[21] was used to study the effect of MMP blockade on survival in a nude mouse model. HPAC cells were grown in Dulbecco's modified eagle medium supplemented with the following: 10% fetal bovine serum, 2 μg/ml insulin, 5 μg/ml transferrin, 40 ng/ml hydrocortisone, 10 ng/ml epidermal growth factor, 1 × antibiotic/antimycotic mixture (Sigma, St. Louis, Mo.). The cells were grown in a humidified atmosphere containing 5% carbon dioxide. Representative confluent plates were counted and confirmed to be more than 90% viable by trypan blue exclusion (Sigma). The cells were then harvested in log-phase growth by scraping and suspended in cold phosphate-buffered saline solution (PBS); a hemocytometer was used to document that the cell population in each inoculum exceeded 10 million cancer cells.

Orthotopic Model of Pancreatic Cancer

Animal protocols with athymic mice and human cancer tissue were approved by the Laboratory Animal Medical Ethics Committee at the University of South Florida and the James A. Haley VA Medical Center in Tampa, Florida. Thirty male Balb-C nu/nu mice (Life Sciences, Inc., St. Petersburg, Fla.) weighing 20 to 25 g were obtained at 3 weeks of age and housed in an approved nude animal facility. The mice were allowed to acclimate to the facility for 7 days prior to manipulation. Twelve-hour light/dark cycles were maintained in the facility, and mice had free access to water and mouse chow. At 4 weeks of age, mice underwent celiotomy under sodium pentobarbital anesthesia (0.05 mg/g) through a midline incision. At the time of celiotomy, the greater curvature of the stomach was mobilized out of the incision and followed distally to the "C" loop of the duodenum where the head of the pancreas was identified. Using a 27-gauge needle, an inoculum of 10 million cancer cells suspended in 0.1 ml of PBS was injected into the parenchyma of the head of the pancreas carefully avoiding injection into the stomach, lumen of the duodenum, or small intestine. The C loop was then carefully placed back into the abdomen, and the wound was closed in a single layer with 5-0 absorbable sutures incorporating the skin, subcutaneous tissues, and peritoneum in the closure. The mice were given time to recover under a heat lamp and allowed to recuperate for 7 days prior to therapeutic intervention.

Treatment and Evaluation of Its Effect on Survival and Metastases

Seven days after implantation of tumor cells, all mice were grouped and randomly selected to receive either the synthetic inhibitor of metalloproteinases, BB-94 (British Biotech, Inc., Annapolis, Md.) or vehicle (PBS containing 0.01% Tween 80). Treated and control animals were dosed daily with 30 mg/kg BB-94 intraperitoneally or vehicle alone for 2 weeks and then changed to every other day dosing for the remainder of the study to minimize the morbidity associated with intraperitoneal injection. The dosage selected was based on previous in vivo experiments using nude mice, which documented biologically active blood levels (12 to 30 ng/ml) that were greater than 10 times the documented IC-50 of this inhibitor of collagenase.[13] Mice were checked daily, weighed weekly, and autopsies were performed as animals died of tumor burden and cachexia. Moribund animals were sacrificed as the study progressed, as mandated by predetermined criteria set forth by the animal ethics committee. Specific criteria included loss of more than 20% maximum body weight, lethargy/failure to respond briskly to noxious (pinprick) stimuli, and failure to rapidly normalize skin turgor after "back pinch" signifying severe dehydration. On day 70, all surviving animals were sacrificed and autopsied in a similar fashion. Autopsies documented the gross and histologic presence of tumor in the orthotopic position, extent of local invasion, and distant metastatic disease (Figs. 1 and 2). Tumors in each group were also stained with hematoxylin and eosin and evaluated for histopathologic differences. As a surrogate marker for tumor burden, animals were weighed prior to autopsy

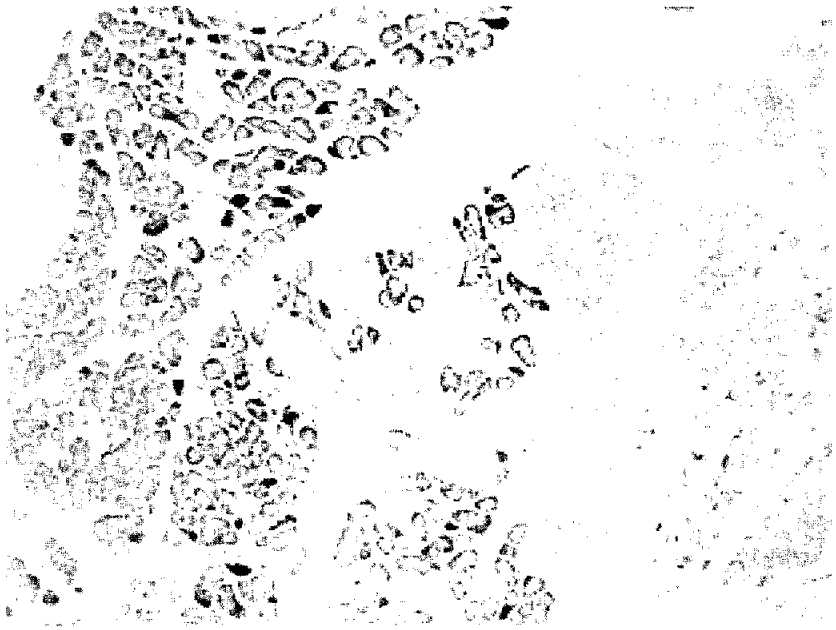

Fig. 1. Histologic verification of human pancreatic cancer allograft orthotopically incorporated into normal murine pancreas.

Fig. 2. Gross appearance of periampullary region of nude mouse at time of autopsy.

and weights in animals with orthotopic tumors were compared between groups. A time line detailing the in vivo segment of the experiment is shown in Fig. 3.

Gelatin Zymography

Representative snap-frozen tumors from animals in each group were thawed at room temperature, and a 100 mg of aggregate tumor tissue was homogenized at 4° C in 0.1 mol/L Tris buffer (pH 8.1) containing protease inhibitors (aprotinin, 100 μg/ml; phenylmethylsulfonyl fluoride [PMSF], 200 μmol/L; and leupeptin, 10 μg/ml [Sigma]). The homogenate was sonicated for 1 minute at 4° C and then spun in an ultracentrifuge at 100,000 × *g* for 45 minutes at 4° C. The supernate was collected, and protein concentrations were determined with the Bio-Rad protein assay reagent (Bio-Rad Laboratories, Inc., Hercules, Calif.).

Gelatin-sepharose (Pharmacia Biotech Inc., Sweden) was washed three times with equilibration buffer (pH 7.5: 50 mmol/L Tris, 150 mmol/L NaCl, 5 mmol/L $CaCl_2$, 0.02% Tween 20, 0.07% Brij 35, and 10 mmol/L EDTA). Twenty microliters of equilibrated gelatin-sepharose was added to 1600 μg of tumor protein extracts and diluted to a final volume of 1 ml with PBS. Samples were then placed on an end-over-end shaker overnight at 4° C to allow the binding of gelatinases to the gelatin-sepharose. Following overnight shaking, nonspecifically bound proteins were washed from gelatin-sepharose with salted equil-

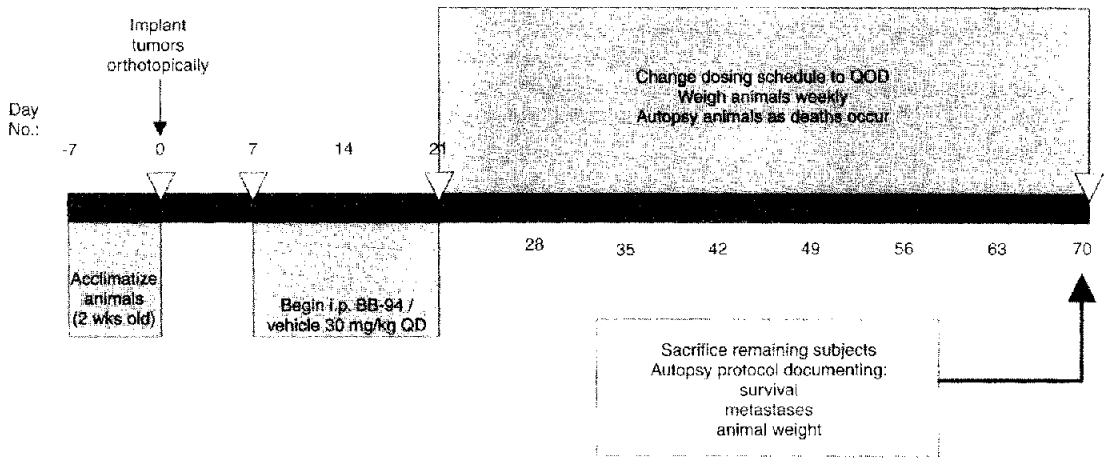

Fig. 3. Time line detailing animal model and treatment protocol for orthotopic model of human pancreatic cancer.

ibration buffer (50 mmol/L Tris, 200 mmol/L NaCl, 5 mmol/L $CaCl_2$, 0.02% Tween 20, 0.07% Brij 35, and 10 mmol/L EDTA), and 15 µl of nonreducing Laemmli was added to the gelatin-sepharose purified samples.

The samples were then diluted 1:4 and electrophoretically separated on 8% SDS-polyacrylamide gel impregnated with gelatin (1 mg/ml). After incubation, the gels were rinsed twice in 2.5% Triton X-100 and three times in double-distilled water. The gels were then incubated at 37° C for 4 hours in 200 mmol/L NaCl, 10 mmol/L $CaCl_2$, 0.07% Brij 35, and 50 mmol/L Tris-HCl buffer, pH 7.4. The gels were stained with 0.05% Coomassie brilliant blue and destained in 10% acetic acid in water. Gelatinolytic enzymes were detected as transparent bands on the background of the Coomassie blue–stained gel. HT 1080 (ATCC CCL-121) cells, known producers of MMP-2 and MMP-9, served as the positive control.[22]

Statistical Analysis and Data Management

Survival, animal weight, and metastases were compared only in animals with documented orthotopic tumors at autopsy (n = 13 BB-94; n = 13 control). Survival curves for each group were compared using the Wilcoxon test, and likelihood of survival to the predetermined end of the study was compared using the Z-test for end points. Invasion/metastases were compared using Fisher's exact test, and animal weights were compared by means of Student's *t* test. Significance was accepted with 95% confidence. Statistical comparisons were not made between treated and untreated animals with regard to MMP activity because tumors had to be pooled within treatment groups to achieve adequate amounts of protein for analysis. Objective comparisons of band density were confirmed, however, using band densitometry (UVP GDS 8000 gel documentation system, Ultra Violet Products, Upland, Calif.).

RESULTS

Tumor Implantation

Tumor implantation was confirmed histologically in 13 of 15 animals in each group. The likelihood of tumor "take" was not statistically different between treated and control animals.

Survival, Metastases, and Tumor Burden

Survival was significantly improved in treated animals when compared to those not treated ($P = 0.03$, Wilcoxon test; Fig. 4). The probability of survival to the predetermined end point of the study (day 70) was also statistically more likely in treated than in untreated animals ($P < 0.05$, Z test for end points).

Furthermore, animals receiving BB-94 weighed significantly more and had less evidence of local invasion/metastatic spread at autopsy than control animals. At autopsy, 9 of 13 animals in the control group developed metastases to the liver, peritoneum, abdominal wall, or local lymph nodes, whereas only 2 of 13 animals in the treated group developed the same ($P < 0.02$, Fisher's exact test, Table I).

Histologic Findings

Blinded histopathologic examination of all tumors, primary and metastatic, confirmed viable moderately differentiated cancer, but no histologic differences were noted between treated and control animals.

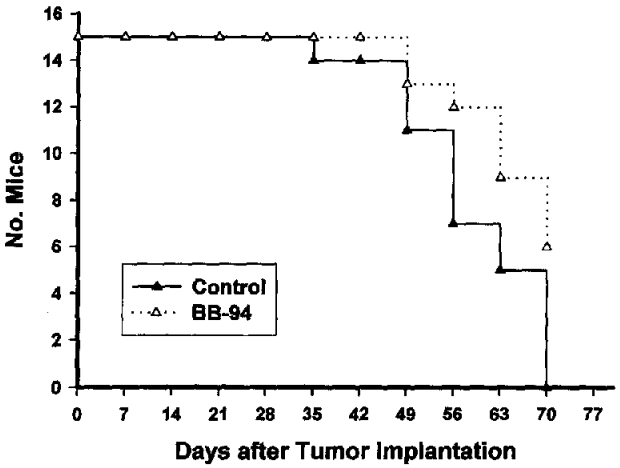

Fig. 4. Survival curve demonstrating improved survival in animals receiving BB-94 vs. animals receiving vehicle control ($P < 0.05$, Fisher's exact test).

Table I. Effect of BB-94 on tumor progression in an orthotopic model of human pancreatic cancer

Group	Animal weight at autopsy (g)	70-day survival	Incidence of local invasion
Control (n = 13)	40 ± 6.2	0/13	9/13
BB-94 (n = 13)	58 ± 7.9*	4/13†	2/13‡

*$P < 0.05$ Student's t test.
†$P < 0.05$ Z-test for end points.
‡$P < 0.05$ Fisher's exact test.

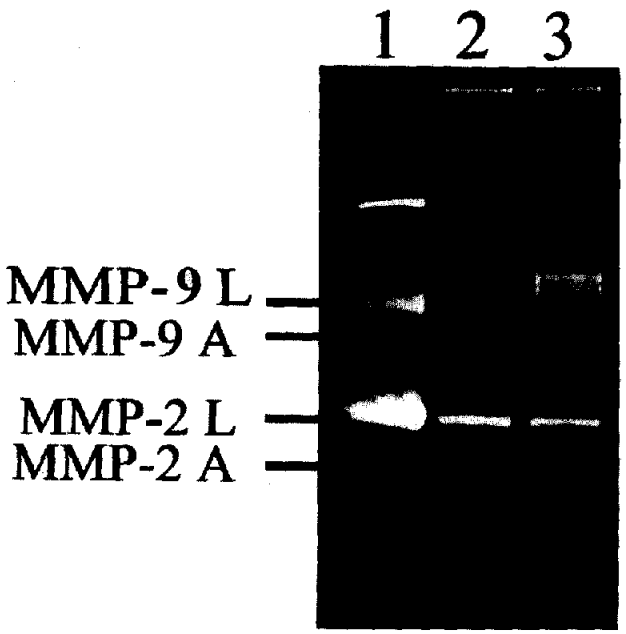

Fig. 5. Gel zymogram demonstrating expression of active and latent MMP-2 and MMP-9 in representative human cancer allografts grown in treated (BB-94) and untreated (control) animals. Lane 1 represents zymographic activity of positive control cells (HT-1080); lanes 2 and 3 represent activity of cells harvested from control and treated animals, respectively.

MMP Activity and Inhibition

Gelatin zymography performed on representative tumors from each group confirmed the presence of latent forms of both MMP-2 and MMP-9 in treated and control animals. Active MMP-9 was present in minimal quantities in tumors harvested from treated and control animals, whereas active MMP-2 subjectively appeared in lower quantities than in tumors harvested from animals treated with BB-94. Band densitometry confirmed this subjective observation (Fig. 5).

DISCUSSION

Given the dismal prognosis associated with unresectable pancreatic cancer, much attention has focused on novel therapeutic strategies. Inhibition of those enzymes thought to be responsible for the ability of tumors to violate established anatomic domains has proved effective in animal models of various human cancers. We have previously shown that MMP blockade improves survival in an animal model when applied before tumor implantation. In this study we demonstrated similar efficacy when metalloproteinase inhibitors were applied in the more clinically relevant scenario of first-line therapy after tumor implantation was confirmed.

Mice with documented tumors treated with the synthetic inhibitor of MMP were more likely to sur-

vive to the end of the study and as a group enjoyed significantly improved survival compared to their untreated counterparts. In addition, metastases documented at autopsy were reduced by almost threefold as compared to control mice. Mice with documented orthotopic tumors also weighed more at autopsy in the treated group signifying less tumor burden and cachexia when compared to the control group.

We believe that the salutary effects afforded by these compounds are the result of nonspecific inhibition of those MMP subtypes commonly found in cancers of gastrointestinal origin. Follow-up in vitro studies carried out in our laboratory have documented an inhibitory effect of BB-94 on both the activity and the activation of MMP-2.[23,24] The absence of histologic disparity between treated and untreated animals suggests that MMP activity may also arise from surrounding reactive tissue as proposed by some investigators.[25-27]

These results support the current and ongoing clinical trials MMP inhibitors in human subjects. Since this study was initiated, the next generation of MMP inhibitors has been introduced that target specific MMPs in an attempt to circumvent toxicity associated with interruption of the physiologic activity of these enzymes: tissue repair and remodeling. Preclinical data regarding which specific MMPs are critical in tumor growth and invasion are still lacking, but their identification may enhance therapeutic targets for this exciting new class of therapeutic agents.

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Development of an In Vivo Tumor-Mimic Model for Learning Radiofrequency Ablation

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Radiofrequency ablation requires accurate probe placement using ultrasound guidance. The purpose of this study was to develop an in vivo tumor-mimic model for learning open and laparoscopic radiofrequency ablation. Tumor-mimics were created in ex vivo porcine livers by injecting a mixture of 3% agarose, 3% cellulose, 7% glycerol, and 0.05% methylene blue, which formed 1 cm hyperechoic, discrete lesions on ultrasound. Open and laparoscopic (using a box-trainer) ablation techniques were practiced. In vivo experiments were then conducted in 10 pigs. Three tumor-mimics were created in each animal using a laparoscopic approach. Lesions were characterized sonographically, ablated using an open (n = 5) or laparoscopic (n = 5) approach, and examined pathologically. An ablation in normal liver tissue was performed as a control. Tissue impedance was recorded. Target creation took 81 minutes per animal and 96% of injections were successful. Tissue impedance (48.8 ± 5.8 vs. 49.6 ± 5.4) and ablation size (25.1 ± 3.4 vs. 24.3 ± 5.1) were not significantly different for controls (n = 8) and tumor-mimics (n = 26), respectively. One animal died of a pulmonary embolism following injection of agarose into a hepatic vein. The agarose-based tissue-mimic creates realistic sonographic targets for learning ultrasound-guided open and laparoscopic radiofrequency ablation in an in vivo model. (J GASTROINTEST SURG 2000;4:620-625.)

KEY WORDS: Radiofrequency ablation, tumor-mimic, ultrasound, laparoscopy, liver surgery

Radiofrequency (RF) ablation has recently gained attention as a method of focal tumor destruction for unresectable liver tumors. A high-frequency current is delivered through an electrode (the RF probe), which is placed into the tumor. The current causes ionic agitation within the tissue, generating heat and causing cell death. Preliminary reports have shown that RF ablation may be effective,[1-6] and may be safer than other focal ablative therapies such as cryotherapy.[7] Additionally, RF ablation uses relatively small (15-gauge) needle electrodes that are amenable to minimally invasive approaches.[6,8]

To effectively destroy a tumor, the RF probe must be accurately placed using ultrasound guidance.[4,5,9] Competency with intraoperative ultrasound requires hands-on practice and a learning curve must be overcome, especially for laparoscopic ultrasound.[6,10,11] The advanced ultrasound skills required for accurate probe placement may be difficult to acquire. Short of practicing in the operating room on actual patients, there is currently no model for learning how to accurately ablate hepatic lesions.

The purpose of this study was to develop a tumor-mimic model in porcine hepatic tissue. Specifically our aim was to develop a model to practice open and laparoscopic RF ablation in both ex vivo and in vivo settings. Simulated hepatic tumors would function as sonographic targets for practicing probe placement and ablation. Ideally the tumor-mimic would have the characteristics listed in Table I.

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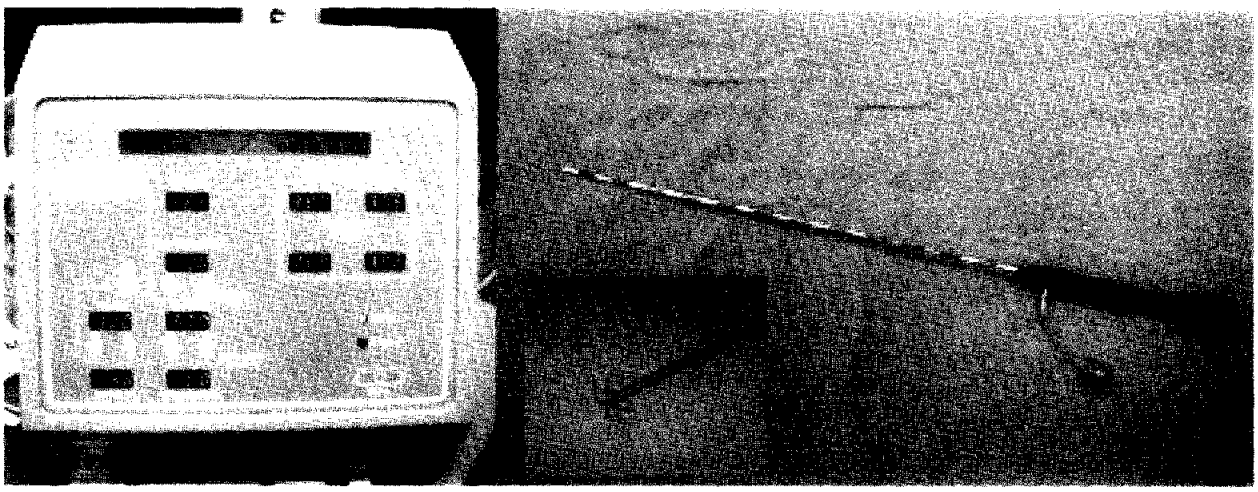

Fig. 1. Radiofrequency generator and probe with four deployable electrodes *(inset)*.

Table 1. Ideal tumor-mimic

Sonographic qualities
Discrete lesions
No acoustic shadowing
Characteristics of radiofrequency ablation
Consistency similar to hepatic tissue
Identifiable on pathologic examination

MATERIAL AND METHODS

Tumor-Mimic Materials

An injectable sonographic phantom was developed to simulate hepatic tumors. Multiple materials, including fibrin sealant, plaster of Paris, epoxy glue, and agarose, were injected into ex vivo porcine liver tissue and characterized sonographically. After initial work with all of these materials, a mixture containing 3% agarose, 3% cellulose, 7% glycerol, and 0.05% methylene blue was chosen.

The mixture was prepared by combining 6 g of agarose, 6 g of cellulose, and 14 ml of glycerol with enough distilled water to make a 200 ml volume. The mixture was then heated to 95° C using a microwave oven to bring its components into solution. Microwave energy on a high-power setting was applied for a total of approximately 5 minutes (for 30 seconds after the solution no longer bubbled intensely). Once heating was complete, 100 mg of powdered methylene blue was added and enough distilled water was added to return the mixture to 200 ml (to restore evaporative losses during heating). Aliquots of 50 ml were transferred to 100 ml glass jars and sealed with air-tight lids. Gradual cooling at room temperature yielded a solid material with a tough gelatin-like consistency. The jars were stored for up to 3 weeks at room temperature prior to use. When needed for an experiment, the 50 ml aliquots were individually reheated in a microwave oven for 1 minute on high power, and then maintained at a temperature of 65° C in a hot water bath.

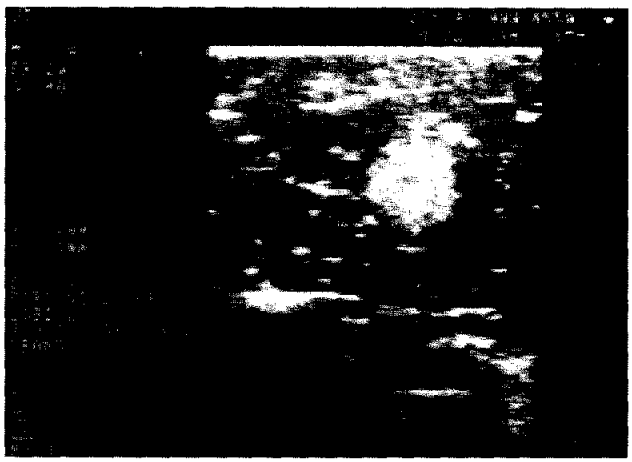

Fig. 2. Ultrasound view of the agarose-based tumor-mimic.

Ex Vivo Radiofrequency Ablation

The agarose mixture was injected at 65° C into ex vivo porcine livers at numerous sites. Maximum liver tissue depth was 3 to 4 cm. A 50-watt RF generator (RITA Medical Systems, Inc., Mountain View, Calif.) was used for all ablations (Fig. 1). Livers were placed on a steel pan with a grounding pad fixed to the undersurface of the pan. A freehand technique was used to place the 25 cm, 15-gauge probe (see Fig. 1) into the center of simulated tumors (Fig. 2) under ultra-

sound guidance (Lynx Ultrasound Unit, B & K Medical, North Billerica, Mass.).

A 7 MHz linear probe was used for the open ultrasound technique (Fig. 3). The liver surface was moistened with saline solution to provide acoustic coupling. A single surgeon (D.J.S.) performed both ultrasound scanning and probe placement simultaneously. The RF probe was guided into the center of the tumor-mimic by initially placing the probe parallel to the ultrasound transducer so that the longitudinal plane was visualized. After guiding the probe to the tumor-mimic center in the longitudinal plane, the transducer was turned 90 degrees so that correct positioning was verified in the transverse plane. Once correctly positioned, four curved electrodes (see Fig. 1, *inset*) were deployed through the RF probe tip.

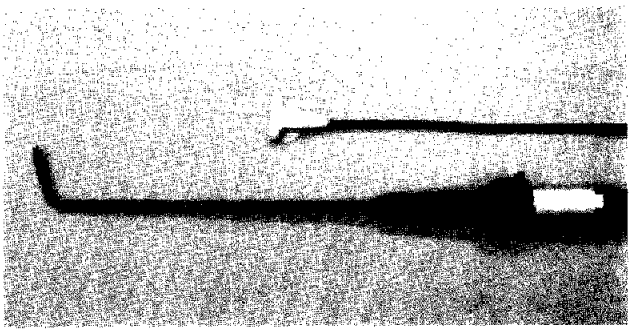

Fig. 3. Open and laparoscopic ultrasound probes.

A standardized protocol was used for all ablations. The RF generator continuously monitored temperature, power, and impedance. Thermistors located at the tips of the four deployed electrodes guided ablation. Maximum power (50 W) was applied until all thermistors reported temperatures above 90° C and the average of the four temperatures was at least 100° C. The generator then delivered a variable amount of power to maintain an average tissue temperature of 100° C for 8 minutes.

A box-trainer (United States Surgical Corp., Norwalk, Conn.) (Fig. 4) and a 7 MHz curvilinear ultra-

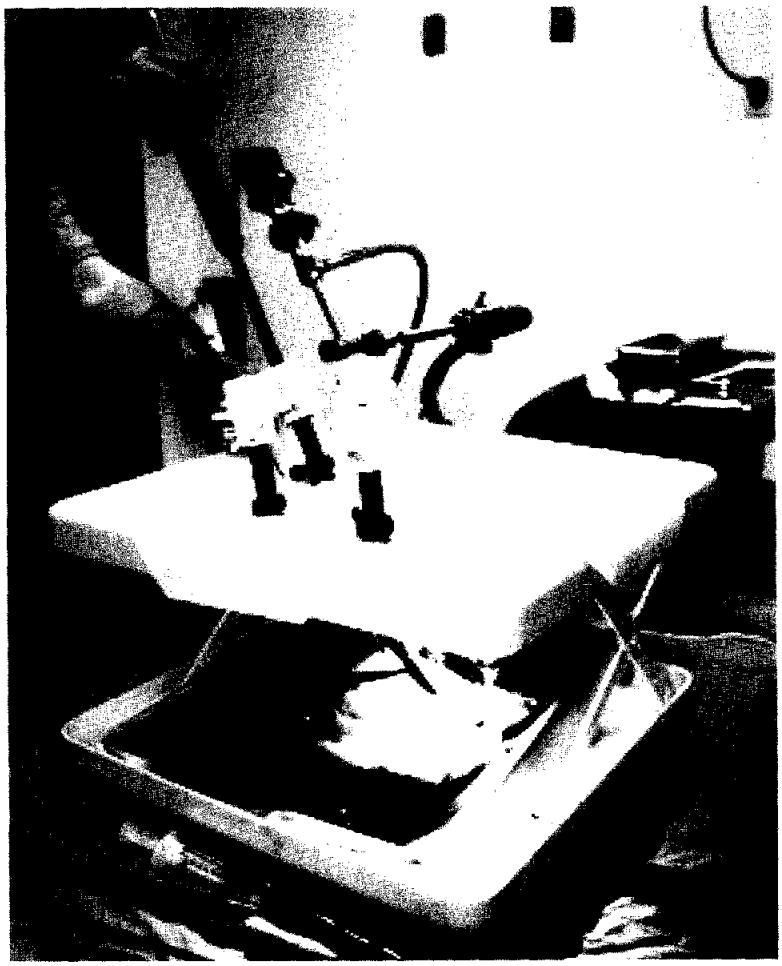

Fig. 4. Laparoscopic techniques were practiced on ex vivo livers using a box-trainer.

sound probe (see Fig. 3) were used to practice the laparoscopic approach. Similar to the open approach, the RF probe was placed parallel to the ultrasound probe. Maintaining the RF probe parallel to the ultrasound probe was critical to accurate placement. The vinyl cover of the box-trainer replicated the abdominal wall and was penetrated by the RF probe. Transfixing the artificial abdominal wall with the RF probe created a pivot point and realistically mimicked the setup required for laparoscopic ablation. The RF probe was positioned 1 to 2 cm toward the surgeon from the ultrasound probe. This configuration allowed the RF probe to be placed into the liver within the acoustic window of the ultrasound probe. Laparoscopic RF probe placement required a surgeon and a radiologist working together. The surgeon (D.J.S.) advanced the shaft of the probe and simultaneously guided the probe tip into the tumor-mimic using a grasper. The radiologist (L.M.W.) performed ultrasound scanning to provide real-time sonographic imaging. Once positioned in the longitudinal plane, a transverse image was obtained by switching the laparoscopic ultrasound probe to a second port. After verifying accurate RF probe placement, RF ablation was performed according to protocol.

Up to eight ablations were performed in each ex vivo liver without overlap. After all ablations were performed, livers were sectioned to confirm that ablations were centered around the simulated tumors, indicating proper probe placement.

In Vivo Radiofrequency Ablation

In vivo experiments were conducted with approval granted by the University of Texas Institutional Animal Review Committee. We created tumor-mimics and performed RF ablation in 10 domestic pigs (mean weight 46 kg) under general endotracheal anesthesia. All procedures were nonsurvival and autopsy was performed immediately postoperatively.

The tumor-mimics were created using a laparoscopic technique. A CO_2 pneumoperitoneum was established to a pressure of 10 mm Hg using a Veress needle. Three to four 12 mm ports were used. A 13 cm, 18-gauge needle was used to inject the agarose mixture. The needle was flushed with sterile water (to prevent injection of air, which would cause shadowing), placed through the skin, and guided into the liver under laparoscopic visualization. Using ultrasound guidance, the needle tip was advanced to a depth of 1.5 to 2.0 cm. Care was taken to avoid injuring vascular or biliary structures with the needle. A 0.7 ml bolus of the agarose mixture heated to 65° C was rapidly injected through the needle into the hepatic parenchyma. The needle was withdrawn and the puncture site cauterized to achieve hemostasis and to prevent extravasation of the liquid-agarose mixture. Three tumor-mimics were created in each animal. Tumor-mimic size and depth, as well as tissue depth, were measured sonographically.

After laparoscopic tumor-mimic creation, animals underwent RF ablation via an open (n = 5) or laparoscopic (n = 5) approach. The port configuration used for tumor-mimic creation was left in place and used for laparoscopic ablations. For the open approach, ports were removed and a bilateral subcostal incision was made. Probe placement was performed as described above for the ex vivo experiments. A grounding pad was fixed to the animal and all three tumor-mimics were ablated. A fourth ablation was performed as a control. The control ablation was performed in an area of normal liver that did not contain a tumor-mimic. Impedance was recorded during all ablations. Immediately postoperatively, livers were harvested and ablated areas were sectioned to determine ablation size.

Ablation size and tissue impedance were compared for control and tumor-mimic ablations using a two-tailed Mann-Whitney U test. Significance was accepted for $P < 0.05$.

RESULTS

Tumor-Mimic Materials

Fibrin sealant infiltrated hepatic sinusoids, creating indistinct and amorphous lesions. Both plaster of Paris and epoxy created discrete hyperechoic lesions, but were associated with intense shadowing and were difficult to inject because of their high viscosity. Agarose by itself produced hypoechoic lesions. The mixture of 3% agarose, 3% cellulose, and 7% glycerol produced discrete hyperechoic lesions with no acoustic shadowing (see Fig. 2). At 65° C, viscosity was low and the mixture was easily injected with an 18-gauge needle. The mixture solidified at approximately 42° C and tumor-mimics were solid in ex vivo (bench livers at 25° C) and in vivo (perfused liver at 37° C) experiments.

Ex Vivo Radiofrequency Ablation

Fifteen ex vivo porcine livers were used to practice open and laparoscopic techniques. All simulated tumors were clearly visible on ultrasound and not felt during penetration by the RF probe. All lesions endured ablation and were readily identifiable on pathologic examination.

Approximately 30 practice ablations were performed using an open approach before we could reliably position the RF probe in the center of the simu-

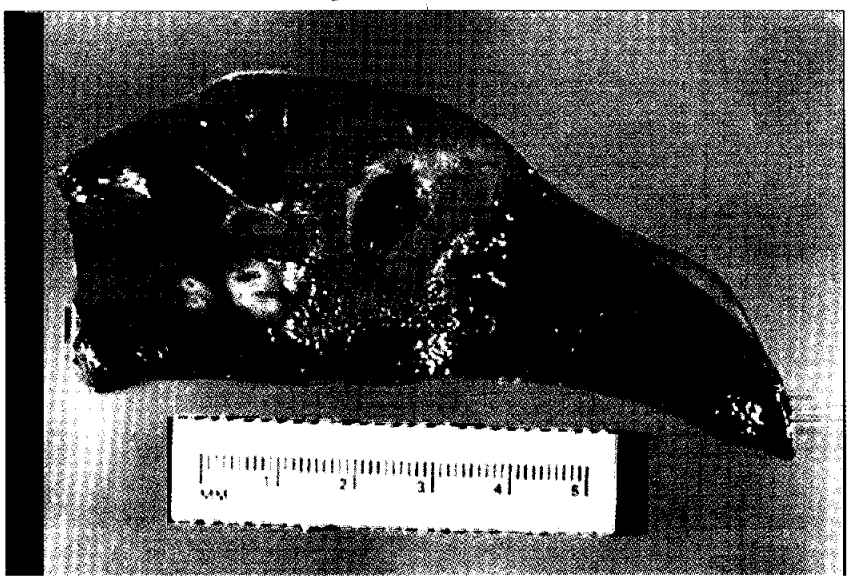

Fig. 5. Gross pathology section of a tumor-mimic ablation. The tumor-mimic (blue) is surrounded by ablated tissue (white) and normal liver (red).

Table II. In vivo tumor-mimic characteristics (n = 26)

Tumor-mimic size (cm)	1.0 ± 0.2
Tumor-mimic depth (cm)	1.6 ± 0.3
Tissue depth (cm)	3.2 ± 0.9

Values are mean ± standard deviation.

Table III. In vivo ablation characteristics*

	Control (n = 8)	Tumor mimic (n = 26)
Tissue impedance (Ω)	48.8 ± 5.8	49.6 ± 5.4
Ablation size (mm)	25.1 ± 3.4	24.3 ± 5.1

Values are mean ± standard deviation.
*$P > 0.05$ for all data; control vs. simulated tumors; Mann-Whitney U test.

lated tumors using ultrasound guidance. After practicing the open approach, we performed an additional 20 ablations using the box-trainer before we could reliably place the RF probe using laparoscopic ultrasound guidance.

In Vivo Radiofrequency Ablation

Simulated tumor creation took 81 minutes (range 72 to 90 minutes) per animal. Injections were successful in 26 (96%) of 27 attempts; one injection extravasated from the liver and did not form a suitable target. One animal died during target creation and the data were excluded. In this animal the agarose mixture was inadvertently injected into a hepatic vein, which caused a fatal pulmonary embolus.

Tumor-mimic characteristics are listed in Table II. On average, injections resulted in 1 cm targets, which were centered in the liver according to depth.

Tumor-mimics were clearly visible as discrete blue lesions surrounded by white ablated tissue (Fig. 5). Tissue impedance and ablation size were not significantly different for control and tumor-mimic ablations (Table III).

DISCUSSION

Agarose-based sonographic phantoms have been reported for other purposes,[12] but have not been described for creating simulated tumors for RF ablation. Agarose is used for Western blot DNA analysis and is widely available. The agarose mixture was simple to make and proved useful. Realistic, durable tumor-mimics were successfully created. In vivo tumor-mimic creation was well tolerated as long as blood vessels were avoided during injection of the agarose mixture. All tumor-mimics were clearly visible on ultrasound and provided suitable targets for ablation. The tumor-mimic was similar enough to liver parenchyma that no difference in consistency was detected during penetration by the RF probe. Accurate probe placement depended solely on ultrasound guidance. Lesions were suitable in size (1 cm) for the limited thickness (3 to 4 cm) of porcine liver. Our data indicate that the agarose mixture did not alter tissue impedance or ablation size. We were able to ablate the tumor-mimics and clearly

identify them on pathologic examination, allowing verification that targets had been successfully hit.

The ex vivo tumor-mimic model provided unlimited practice using ultrasound guidance. Experience was gained aligning the RF probe in the appropriate plane to effectively use sonographic imaging for guidance. These maneuvers were not intuitive and had to be learned. Thirty open ablations were required before accurate probe placement was reliably performed. The laparoscopic approach was associated with an additional learning curve; 20 ablations were performed in the box-trainer before tumor-mimics were reliably targeted.

The in vivo tumor-mimic model added realistic space confines (costal margin, abdominal wall, diaphragm, etc.), anatomic variability, and blood flow. In vivo RF probe placement was considerably more difficult than ex vivo placement. Motion artifact secondary to respirations had to be overcome. Anatomic structures (blood vessels and bile ducts) had to be avoided. The added degree of difficulty and increased realism made the in vivo model particularly well suited for training.

RF ablation is a promising new technology but requires significant expertise for accurate probe placement. Advanced skills must be mastered before RF ablation can be safely performed on patients. For novice ultrasonographers, considerable practice is needed before competency is achieved, especially with the laparoscopic approach. Practicing in the operating room may place patients at risk and is expensive.

The tumor-mimic model is simple, inexpensive, and effective. The agarose mixture costs less than $200 for the entire study. An ex vivo liver costs $4 and each in vivo procedure costs approximately $200. The tumor-mimic model offers unlimited practice in a safe, controlled environment. This model may be useful for surgeons in practice who need to improve their skills. Similarly, surgery residents can be effectively trained using the model in a skill laboratory setting. The tumor-mimic model may be useful for learning RF ablation, intraoperative ultrasound, and freehand biopsy techniques. This model may also be useful for investigations concerning the efficacy of RF ablations in achieving tumor-free margins.

CONCLUSION

RF ablation requires advanced sonographic skills for accurate probe placement. The agarose-based tumor-mimic model effectively, economically, and safely facilitates practicing RF ablation in ex vivo and in vivo porcine livers.

Equipment was provided by RITA Medical Systems, Inc., Mountain View, California, and B&K Medical, North Billerica, Massachusetts.

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Achalasia Developing Years After Surgery for Reflux Disease: Case Reports, Laparoscopic Treatment, and Review of Achalasia Syndromes Following Antireflux Surgery

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Two case reports demonstrate the paradoxical occurrence of achalasia many years after the successful surgical treatment of gastroesophageal reflux disease (GERD). These patients had remedial surgery laparoscopically. The three types of achalasia syndromes that can follow antireflux surgery are discussed. In type 1, primary achalasia is misdiagnosed as GERD and inappropriate antireflux surgery causes worsening dysphagia immediately after surgery without any symptom-free interval. In type 2, secondary iatrogenic achalasia is seen early after antireflux surgery and is characterized by the presence of stenosis and scar formation at the site of the fundic wrap. Although the motility studies resemble achalasia, the repair needs only to be taken down and refashioned when there is no response to balloon dilatation. In type 3, illustrated by the case reports, primary achalasia follows antireflux surgery after a significant symptom-free interval. There is complete absence of any stenosis or fibrosis of the esophagus and periesophageal tissues at remedial surgery. Moreover, surgical treatment of this condition needs to include esophageal myotomy. (J GASTROINTEST SURG 2000;4:626-631.)

KEY WORDS: Achalasia, laparoscopic surgery, gastroesophageal reflux

Achalasia is a motor disorder of the esophagus that is characterized clinically by dysphagia, radiographically by dilatation of the esophagus with smooth "bird-beak" distal narrowing, and manometrically by failure of the lower esophageal sphincter (LES) to relax and by impaired peristalsis. So far, the disease has been classified as primary (or idiopathic) achalasia, representing a disorder of unknown etiology with ganglion cell degeneration of the esophageal myenteric plexus. Secondary achalasia (or pseudoachalasia) defines a similar obstructive syndrome of the lower esophagus associated with multiple conditions including infection (Chagas' disease), cancer, intestinal pseudoobstruction, encephalitis, diffuse esophageal leiomyomatosis, sarcoidosis, pancreatic pseudocyst, familial adrenal insufficiency and alacrima, amyloidosis, Fabry's disease, eosinophilic infiltration, sicca syndrome with gastric hyposecretion, multiple endocrine neoplasia (type 2b), multiple congenital defects, and fibrotic narrowing following hiatal surgery.[1-12]

We describe two patients who were diagnosed with gastroesophageal reflux disease (GERD), and were medically and surgically treated for it. Years later they developed achalasia unrelated to postoperative fibrosis or stenosis secondary to the previous hiatal surgery. Their reoperations were done laparoscopically. We also review the literature concerning the apparent paradoxical coexistence of esophageal reflux and achalasia of the esophagus and the differences between patients with secondary achalasia following hiatal surgery and the patients presented in this report. Based on these differences, we suggest a classification of achalasia syndromes that follow antireflux surgery.

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CASE REPORTS

Case 1

A 69-year-old woman had a long history of esophageal problems. At age 38 she underwent a posterior fundoplication for gastroesophageal reflux and was symptom free for many years. Gradually symptoms of dysphagia developed, which eventually required multiple episodes of passive dilatations. Her symptoms were ascribed to postoperative scarring at the hiatal surgery site. She was able to maintain her weight, but by age 67 her symptoms had worsened and required further investigation.

An esophageal motility study and upper gastrointestinal barium swallow confirmed the presence of achalasia. Her LES pressure was 50 mm Hg, with incomplete relaxation during voluntary swallows. She had nonperistaltic contractions after 60% of the swallows. Botulinum toxin (80 U) was injected locally at the LES with good results lasting for 6 months. Her symptoms recurred, and after failure of repeat botulinum toxin injections, she was referred for surgery. At age 69, which was 31 years after the initial antireflux surgery, she underwent a laparoscopic takedown of the posterior fundoplication and a 7 cm laparoscopic esophageal myotomy.

At surgery no evidence was seen of fibrotic sequelae involving the esophagus and the periesophageal tissues or stricture from the previous surgery, as evidenced by easy passage of a 50 F Maloney bougie. There was no evidence of slippage or breakdown of the previous repair. Intraoperative esophagoscopy was used to ensure that the myotomy was not carried on to the stomach. Because the myotomy did not involve the stomach and the esophagus was aperistaltic, an antireflux procedure was not performed. Postoperatively she immediately recovered her ability to swallow. Six months later she started to experience occasional symptoms of reflux, which responded to sporadic administration of oral ranitidine. Because of her age, the infrequent occurrence of her symptoms, and the response to anti-H_2 blockers, she refused esophageal motility studies and 24-hour pH studies. An upper gastrointestinal barium series showed normal progression of barium, a small reducible hiatal hernia, and no stenosis (Fig. 1). She later lost 15 pounds, and her occasional heartburn disappeared. She remains free of dysphagia 30 months after corrective surgery.

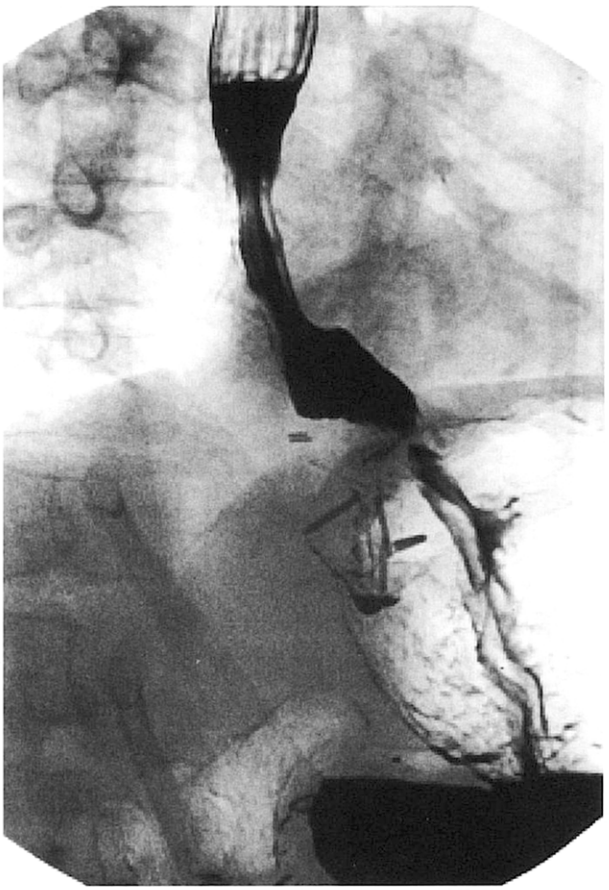

Fig. 1. Barium series in a 69-year-old woman 6 months after reparative laparoscopic myotomy showing normal progression of barium, a small reducible hiatal hernia, and no stenosis.

Case 2

At 27 years of age, this 39-year-old man had an open Collis-Nissen gastroplasty for severe reflux disease and associated ulcerative esophagitis. Preoperative motility studies showed a weak LES. He was well for 2 years but slowly began to experience increasing dysphagia, first to solids, then to liquids. Symptoms were relieved by multiple passive dilatations with Maloney bougies, allowing him to maintain his weight. Initially the dilatations were spaced 1 year apart; however, the increasing severity of his symptoms required more frequent dilatations and prompted further investigation. Two esophageal motility studies 4 months apart with cholecystokinin injection at the latter examination were compatible with achalasia or postoperative stricture. The mean pressure at the level of the LES was 50 and 68 mm Hg, with residual pressures of 30 and 40 mm Hg, and incomplete relaxation. Some normal peristaltic waves were observed in the body of the esophagus. The fact that the zone relaxed normally with cholecystokinin would have suggested postoperative stricture rather than achalasia. Barium studies showed a dilated esophagus with a short, tight stricture at the level of the previous repair (Fig. 2). Endoscopy was compatible with a slipped Nissen fundoplication with the extrinsic indentation associated with the repair situated well below the esophagogastric junction, but this was difficult to ascertain with the presence of the Collis gastroplasty tube easily giving the appearance of a slipped repair.

Twelve years after the initial surgery, this patient underwent a laparoscopic takedown of his previous Collis-Nissen gastroplasty, and the lower end of the esophagus was found to be devoid of any fibrosis that could explain a late postoperative stricture, as evidenced by easy passage of a 50 F Maloney bougie. There was no evidence of slippage or breakdown of the previous repair. The lower end of the esophagus appeared intact. A 7 cm myotomy was performed, and the previous wrap was maintained posteriorly

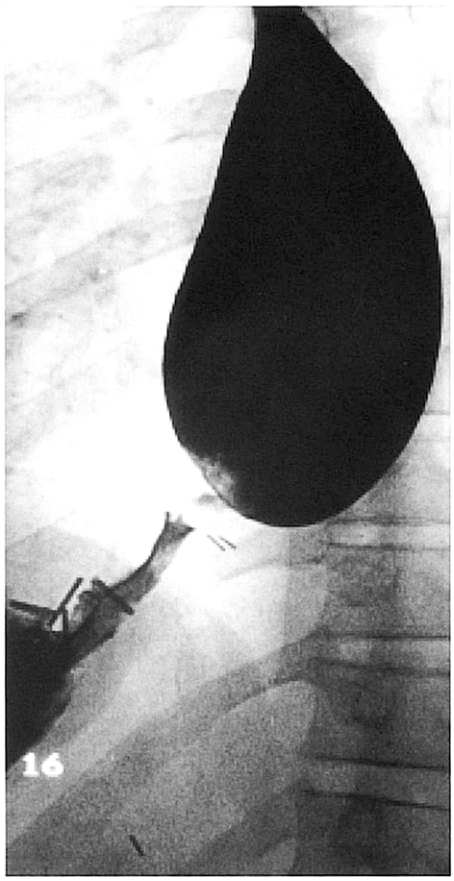

Fig. 2. Preoperative barium series (posterior view) in a 39-year-old man 12 years after a Collis-Nissen procedure shows a dilated esophagus and a short, tight stricture at the gastroesophageal junction.

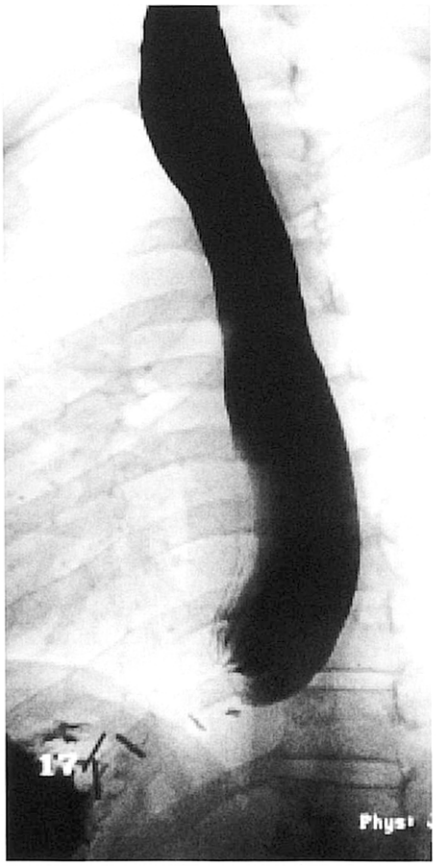

Fig. 3. Same patient as in Fig. 2. Repeat barium series (posterior view) 6 months after surgery shows normal progression of the contrast medium and significantly less distention than on preoperative examination.

as a Toupet posterior plication because the patient had exhibited some esophageal peristalsis in his preoperative motility study. Intraoperative endoscopy was used to identify the esophagogastric junction with precision; however, identification was more difficult because of the previous Collis gastroplasty. The myotomy incision was not carried into the stomach tube. The patient recovered the ability to swallow normally and became asymptomatic. Six months after surgery, a repeat barium series showed normal progression of the contrast medium and significantly less distention than on the preoperative examination (Fig. 3). The 24-hour pH study showed acid exposure in the esophagus less than 1% of the total study time (normal ≤4%) and a DeMeester score of 3 (normal ≤18). An esophageal motility study revealed a LES pressure of 12 mm Hg and normal relaxation; occasional peristaltic waves were observed. He remains asymptomatic 20 months after his remedial surgery.

LAPAROSCOPIC TECHNIQUE

Laparoscopic reparative surgery of the esophageal hiatus requires patience, especially when the primary surgery was performed in the traditional open fashion. A 15 mm Hg pneumoperitoneum is created through an open-entry technique at the umbilicus. It is important to dissect adequately under direct vision to ensure an atraumatic entry into the peritoneal cavity. The patient is placed in a steep reverse Trendelenburg position. A five-trocar setup is used with three 12 mm trocars: one in the umbilicus; two in each of the upper abdominal quadrants, a 5 mm trocar near the right side of the xyphoid process, which serves to retract the left lobe of the liver; and another 5 mm trocar placed in the left flank, which serves as a retractor of the stomach or the esophagus. After placement of the umbilical trocar, the severity and location of adhesions dictate which trocar will be inserted next under direct vision. A bougie is placed in the esophagus when its location is unclear. Adhesions are dissected and commonly involve omental tissues with the posterior aspect of the previous abdominal incision. To minimize bleeding and cautery use, it is preferable to carry this dissection in areolar planes whenever possible and as close to the peritoneum as possible. As the operative field clears, the remaining trocars are placed under direct vision. When the patient has had a previous Nissen fundoplication, it is usually easier to create a dissecting plane between the anterior part of the esophagus and the fundoplication. It is then easy to identify where the previous repair was sutured and to take it down using a linear stapler. With this maneuver it is easier to define the rest of the hiatal anatomy under direct vision; special care is given to sparing the vagus nerves. In the case of a previous repair, it is dangerous and more difficult to begin the dissection by redefining the left border of the right crux and from there to identify the esophagus or the gastric fundus; this leads to more frequent iatrogenic perforations (Fig. 4). It is essential to avoid any blind dissection and the use of clamps or retractors directly on the esophagus. The esophagus can be lifted safely from its underside or retracted by a previously placed Penrose drain. The corrective surgery then follows all the principles accepted in traditional open surgery, which are well described in the works of Ellis et al.[13] and Stuart and Hennessy.[14]

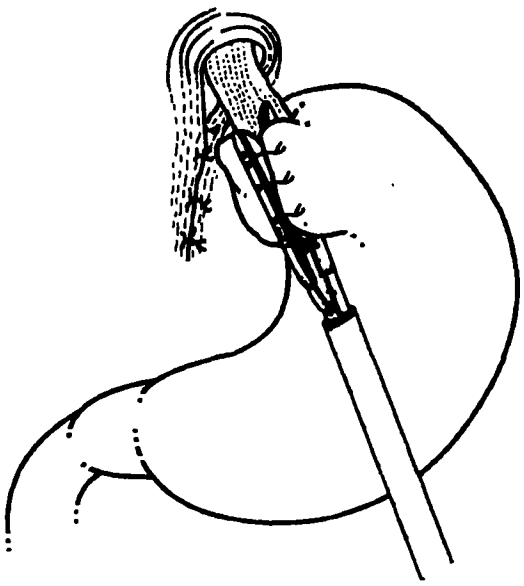

Fig. 4. For reparative surgery, dissection is avoided on the left side of the right crux because of an increased risk of esophageal and stomach perforation at the site of previous repair. Preferably the previous repair is dissected and stapled precisely at the former suture line. The freed stomach is used to delineate the anatomy more safely.

DISCUSSION

The synchronous or metachronous occurrence of gastroesophageal reflux and achalasia outside the confines of esophageal dilatation or myotomy constitutes a rare phenomenon that seems paradoxical. Smart et al.[15] described five patients presenting with symptomatic gastroesophageal reflux, proven by radiologic studies or pH monitoring, who subsequently developed achalasia confirmed by radiology and manometry after an interval of 2 to 10 years. They concluded that gastroesophageal reflux do not protect against the subsequent development of achalasia and suggested that the autonomic nerve damage eventually leading to achalasia may in its initial phases cause gastroesophageal reflux. More recently Shoenut et al.[16] studied 48 consecutive untreated achalasia patients. All of their patients underwent 24-hour pH studies,

Table I. Achalasia and achalasia-like syndromes after antireflux surgery

Type	Description	Appearance of symptoms	Symptom-free interval	Status of esophagus at surgery
1	Synchronous primary achalasia (misdiagnosed as GERD)	Early postoperatively	No	Normal
2	Secondary achalasia	Early postoperatively	No	Fibrosis, stricture of repair
3	Metachronous primary achalasia	Usually years after surgery	Yes	Normal

GERD = gastroesophageal reflux disease.

which showed abnormal acid exposure in 20%. Gastroesophageal reflux is therefore known to occur as a distinct entity preceding the diagnosis of primary achalasia. Acid exposure of the lower esophagus in patients already diagnosed with esophageal achalasia also has been described.[17]

As to achalasia developing after antireflux surgery, the clinical picture and classification are more confusing. Three types of achalasia syndromes are seen after antireflux surgery, and we suggest a classification that takes into account the differences between each type. Type 1 refers to patients with "heartburn," "spasm," and dysphagia who are misdiagnosed as having gastroesophageal reflux and thus undergo an antireflux procedure when, in fact, they have primary achalasia. Their dysphagia gets worse after surgery. This generally occurs in patients who did not have preoperative esophageal motility studies; some undergo inappropriate fundoplication. Failure to perform preoperative esophageal manometry in patients being considered for antireflux surgery can result in immediate persistent postoperative dysphagia due to a missed diagnosis of achalasia. Patients with synchronous achalasia misdiagnosed as GERD who have had inappropriate fundoplication have been successfully treated with balloon dilatation or surgery.[12,18,19] Type 2 refers to some patients who develop persistent postoperative dysphagia. This is different from the transient dysphagia that occurs in 40% to 70% of patients after fundoplication and is thought to be secondary to swelling in the area of the gastroesophageal junction or transient esophageal hypomotility. Fortunately this dysphagia usually resolves spontaneously within 2 to 3 months and does not require extensive investigation. Investigation is indicated for patients with persistent dysphagia and a few will be found to have a type 2 achalasia syndrome.[20] Their presentation seems similar to that of type 1 in that there is no symptom-free interval. However, these patients are found to have iatrogenic secondary achalasia (i.e., pseudoachalasia) resulting from postoperative fibrosis or stenosis at the operative site. They often require takedown of the stenotic antireflux repair and construction of a loose wrap. Some patients also respond to balloon dilatation.[11] Type 3 refers to patients, such as those described in this report, who develop achalasia long after their hiatal surgery for reflux. At surgery no fibrotic process or stenosis is demonstrated to justify their classification as secondary achalasia, and the achalasia syndrome cannot be demonstrated to be related to hiatal surgery. They require myotomy at remedial surgery (Table I).

We therefore suggest a classification of achalasia syndromes that follow antireflux surgery into three types. There is a need to underscore the differences in etiology and treatment of achalasia-like syndromes that follow antireflux surgery (see Table I). It should not come as a surprise that occasionally patients who are properly investigated for GERD will undergo antireflux surgery and then develop achalasia much later on; however, these patients must be distinguished from patients who develop secondary achalasia early after hiatal surgery. Patients such as those in this report tend to present with dysphagia long after the initial hiatal surgery and after a significant period without postoperative dysphagia. Furthermore, at surgery the esophagus appears normal and presents no evidence of the type of fibrosis, scarring, or stenosis seen in iatrogenic postoperative secondary achalasia. Despite the long symptom-free interval, patients such as these are considered initially to have a complication of antireflux surgery, and this is not the case. Unlike patients with secondary achalasia following antireflux surgery (type 2), they do not require simple takedown and refashioning of their repairs. An esophageal myotomy is necessary.

For these reasons we have defined three sets of circumstances where achalasia follows antireflux surgery. Patients show early or late onset of symptoms after surgery with or without a symptom-free interval. They also differ by the status of the esophagus and periesophageal tissues at remedial surgery with pres-

ence or absence of fibrosis or stenosis. They may or may not require esophageal myotomy as part of their reparative treatment.

CONCLUSION

The diagnosis and laparoscopic management of two patients who presented with esophageal achalasia many years after successful surgery for GERD are presented. The presentation differs markedly from the secondary achalasia seen after antireflux surgery by the presence of a significant symptom-free interval with an absence of any fibrosis, scarring, or stenosis of the esophagus and periesophageal tissues at surgery. These patients also contrast with patients who are misdiagnosed as having GERD and therefore undergo inappropriate antireflux surgery. In these patients the dysphagia often worsens in the immediate postoperative period and is not caused by undue scarring around the surgical repair. A classification of achalasia syndromes following antireflux surgery is presented and reflects these differences.

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Functional Results After Laparoscopic Rectopexy for Rectal Prolapse

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We investigated the functional results after laparoscopic rectopexy for rectal prolapse in 29 patients at least 12 months postoperatively. Twenty patients were evaluated completely pre- and postoperatively (median 22 months postoperatively, range 12 to 54 months). Six patients were interviewed by telephone, two patients were lost to follow-up, and one patient died of causes unrelated to rectal prolapse. Patients underwent a proctologic examination, anoscopy, rigid sigmoidoscopy, fluoroscopic defecography, and anorectal manometry pre- and postoperatively, and an additional standardized interview postoperatively. Anorectal manometry showed a significant increase in maximum anal resting and squeeze pressures postoperatively (resting pressure 72 ± 8 vs. 95 ± 13 mm Hg, pre- vs. postoperatively; $P = 0.046$; squeeze pressure 105 ± 17 vs. 142 ± 19 mm Hg, pre- vs. postoperatively; $P = 0.035$), and continence improved postoperatively (Wexner incontinence score 6.0 ± 1.0 vs. 3.9 ± 0.8 pre- vs. postoperatively, $P = 0.02$). Twenty (77%) of 26 patients were satisfied with the operative result, but functional morbidity was observed in four patients, with two patients complaining of severe evacuation problems. Rectal prolapse recurred in one patient 42 months postoperatively (recurrence rate 1 [3.8%] of 26 patients). Functional results were very similar to those obtained after open rectopexy, with symptoms of prolapse and incontinence improved in the great majority of patients. (J GASTROINTEST SURG 2000;4:632-641.)

KEY WORDS: Rectal prolapse, intussusception, laparoscopic rectopexy, functional results, anorectal manometry

Rectal prolapse causes a variety of symptoms including outlet obstruction, rectal or perianal pain, transanal bleeding, increased mucous discharge, urge to defecate, incomplete evacuation, and incontinence. Diarrhea, constipation, or a combination of both are often reported in patients with rectal prolapse.[1-5] Rectal prolapse appears to be a true intussusception of the rectum through the sphincters and is associated with a deep rectovaginal or rectovesical peritoneal pouch of Douglas, loose lateral ligaments of the rectum, a loss of attachment of the rectum to the sacrum, a perineal descent that can affect the pudendal nerve, and a diastasis of the levator ani muscle, eventually resulting in rectal prolapse through the anal canal.[1-3,5] Vaginal prolapse, uterine descent, and cystoceles are associated abnormalities that often cause urinary incontinence.[2,3]

A multitude of operations have been described to treat these patients, since rectal prolapse cannot be cured by conservative management.[2-5] In general, rectal prolapse surgery can be performed transanally or transabdominally, either alone or in combination with resection of the sigmoid colon. Posterior approaches include plication of the rectal muscle layers (Délorme procedure) or transanal rectosigmoid resection in combination with a pelvic floor repair (Altemeier procedure), but high recurrence rates of up to about 40% have been reported for both procedures.[2,4-7]

The overall results of the transabdominal operations seem to be better than those of the posterior procedures, with recurrence rates of 2% to 10% being reported.[2,4,5,8] Anterior rectopexy, by encircling the rectum with a sling of artificial material (Ripstein operation), has shown good results with respect to re-

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currence, but postoperative constipation is quite often a problem and the rectum may become constricted.[2,9] Posterior rectopexy was introduced by Wells and included in its original description a division of the lateral ligaments.[2,10] The procedure achieves results similar to those of anterior rectopexy with respect to recurrence, but seems to carry a lower risk of severe evacuation problems.[2,9]

In recent years, a laparoscopic transabdominal approach has become technically feasible. Thus the operative trauma is most likely diminished as a result of reduced morphine requirements, earlier tolerance of solid food, and earlier discharge from the hospital. A decreased incidence of postoperative ileus has also been reported in comparison to historical controls.[11,12] However, no trial has ever been conducted comparing the open abdominal approach with the laparoscopic procedure. It is unlikely that such a trial will ever be launched, since patients would most likely choose the laparoscopic operation once that option was offered, and they would be unwilling to be randomly assigned to undergo laparotomy. A practicable way out of this dilemma is to carefully evaluate the results of laparoscopic rectopexy operations, which should at least match the results obtained by open surgery for rectal prolapse. We therefore investigated the functional results in our patients at least 1 year after laparoscopic rectopexy for rectal prolapse.

PATIENTS AND METHODS

Patients

Between January 1993 and August 1997, a total of 29 patients with rectal prolapse were treated by laparoscopic rectopexy. Patients underwent a proctologic examination, anoscopy, rigid sigmoidoscopy, fluoroscopic defecography, and anorectal manometry pre- and postoperatively, and an additional standardized interview postoperatively. Complete postoperative follow-up was achieved in 20 patients (69%). Follow-up was incomplete for nine patients. Six patients were interviewed by telephone, but did not want to come to the hospital (three patients because of the great distance, one patient with a depressive disorder, one patient with a newborn infant, and one patient without a specific reason). Two patients were lost to follow-up (no current address available for one patient living abroad and one homeless patient), and one patient died in April 1997 of causes unrelated to rectal prolapse.

Of those patients with complete postoperative follow-up, 18 (90%) were female with a mean age of 55 years (median 60 years, range 27 to 82 years) at the time of follow-up. Six were nulliparous (33%), but 10 (56%) had had complications of childbirth with possible damage to the pelvic floor (4 women with one, 5 with two, and 1 with three complicated deliveries). Two patients were males, 26 and 30 years of age, respectively. The median postoperative follow-up was 22 months (range 12 to 54 months). Twelve of 20 patients were operated on for complete (external) rectal prolapse and 8 of 20 for incomplete (internal) rectal prolapse (intussusception). Four patients had a solitary rectal ulcer, which bled repeatedly in two of them. All patients were symptomatic; the main complaints are listed in Table I.

Surgical Technique

The operation used in all patients was an adaption of the procedure introduced by Wells,[10] which includes complete mobilization of the rectum down to the pelvic floor including the division of the lateral

Table I. Symptoms in patients with rectal prolapse (n = 20) pre- and postoperatively

Symptoms	No. of patients	
	Preoperatively	Postoperatively
Pruritus ani	7	2
Soiling	7	1
Regular wearing of pads	7	3
Frequent change of underwear	9	5
Transanal bleeding	2	0
Pain during defecation	5	0
Feeling of rectal prolapse	12	1
Incontinence for gas	13	8
Incontinence for liquid stool	11	7
Incontinence for solid stool	5	4
Constipation	8	10
Diarrhea	5	2
Frequent urge to defecate	8	9
Incomplete evacuation	9	9

ligaments. A 5 × 8 cm polypropylene mesh (Prolene, Ethicon, Inc., Hamburg, Germany) was fixed to the anterior fascia of the sacrum with nonabsorbable sutures (Ethibond 2/0, Ethicon). The mobilized rectum was pulled up and sutured to the mesh, with the mesh forming a trough and covering the dorsal half of the rectal circumference, thereby fixing the lower part of the rectum to the fascia of the sacrum at the level of the promontory. No resection of the sigmoid colon was performed.

Standardized Interview

All 20 patients with complete postoperative follow-up had a standardized interview, which included a total of 77 questions. Eighteen questions were related to prolapse symptoms, 18 questions to social life restrictions, 16 questions to continence, 11 questions to constipation problems, and two questions to satisfaction with the postoperative result. The 12 remaining questions concerned issues not directly related to rectal prolapse, such as general health status, previous operations, or current medications. The answers regarding prolapse, continence, constipation, and social life restrictions were divided into five categories (never, rarely, sometimes, usually, always), and given a score of 0 (best result) up to 5 points (worst result). From the interview, the Wexner incontinence score was obtained (0 points = full continence; 20 points = totally incontinent).[13] In addition, an overall satisfaction score ranging from 0 (very satisfied) to 62 points (completely dissatisfied) was calculated. Finally, patients were asked to grade their postoperative satisfaction on a scale of 1 (completely dissatisfied) to 10 points (very satisfied). This score was not included into the overall satisfaction score.

Anoscopy and Rigid Sigmoidoscopy

All 20 patients underwent proctologic examination, anoscopy, and rigid sigmoidoscopy performed in the lithotomy position. No enemas were given prior to testing. A complete (external) rectal prolapse was diagnosed when a full-thickness rectal protrusion beyond the anal canal was observed on straining of the patient. An incomplete (internal) rectal prolapse (intussusception) was diagnosed when a protrusion of the rectal wall into the anal canal, but not beyond the anal verge, was observed on straining of the patient, with the tip of the proctoscope positioned at the lower part of the anal canal.

Anorectal Manometry

Anorectal manometry was performed as described previously.[14-16] At our anorectal function laboratory, we have established normal manometric values, obtained from healthy subjects, for maximum anal resting pressure (90 ± 40 mm Hg) and maximum anal squeeze pressure (160 ± 60 mm Hg) that are very similar to those reported by others.[17] In brief, anorectal manometry was performed without bowel preparation, with patients investigated in a semirecumbent position. An eight-channel water-perfused manometry system (Arndorfer Medical Specialities Inc., Greendale, Wis.), continuously perfused with 0.1 ml/channel/min, and a standard catheter (ARM^{3}8 standard anorectal catheter, Arndorfer Medical Specialities) were used. The catheter was connected to eight pressure transducers (Statham transducer, model P23XL, Spectramed, Inc., Oxnard, Calif.) to convert pressure signals into electrical signals, which were transmitted to personal computer via an A/D converter (Combi-Interface, PC-Polygraf VIII, Synectics Medical, Frankfurt, Germany). Data storage and evaluation were performed with dedicated software (Polygram Software, version 4.21, Synectics Medical).

Maximum anal squeeze pressure was measured stationary, with the manometry catheter positioned in the high-pressure zone identified by asking the patient to cough, and maximum anal resting pressure was determined by continuous pull-through (speed 1 mm/sec). Thresholds for the patient's first sensation, urge to defecate, and intolerable volume (pain) were determined by rectal balloon distention. Rectal compliance was assessed at maximum tolerable volume. Complete pre- and postoperative original data were obtained for 17 of the 20 patients. In two patients, preoperative manometry data were lost, and in one patient the preoperative maximum anal resting pressure was missing.

Fluoroscopic Defecography

For fluoroscopic defecography, lateral x-ray films of the anorectum were taken with the patient having the rectum filled with a semisolid barium paste (usually about 150 to 180 ml) and sitting on a radiolucent commode. A standardized sequence of x-ray films was obtained during rest, squeezing, straining, and defecation of the barium paste as described previously.[15,18] A radiopaque centimeter ruler was positioned on the film for visualization on the films and for measuring pelvic floor ascent or descent during squeezing and straining. The effective dose equivalent of defecography has been estimated at 4.9 mSv for women and 0.6 mSv for men.[19] Evaluation of the films was carried out by a radiologist who was unaware of the patient's history and included radiologic diagnosis of complete or incomplete rectal prolapse or rectocele. The central anorectal angle was measured during rest and during

defecation, and the pelvic floor ascent and descent on squeezing and straining, respectively.[17,18,20] The anteroposterior diameter of all rectoceles was measured, set in relation to the centimeter ruler on the x-ray film, and given in centimeters. Results of pre- and postoperative fluoroscopic defecography were evaluated in 16 patients.

Statistics

Comparisons were made between pre- and postoperative values using the Mann-Whitney U test (Wilcoxon rank-sum test) and the JMP statistical software package (SAS Institute, Cary, N.C.). A probability value of $P < 0.05$ was considered significant.

RESULTS

Standardized Interview

Most patients reported a decrease in their symptoms with respect to a sense of prolapse, pruritus ani, soiling, the need to wear pads, pain during defecation, transanal bleeding, and anal incontinence, but were less satisfied with symptoms related to incomplete evacuation, urge to defecate, constipation, and diarrhea (see Table I). On a scale grading patients' satisfaction with their operative results ranging from one (completely dissatisfied) to 10 (very satisfied), patients' scores averaged 6.9 ± 0.7 points. Twelve of 20 patients were very satisfied or satisfied (8 to 10 points), 4 of 20 were moderately satisfied (5 to 7 points), and 4 of 20 were dissatisfied (1 to 4 points). When asked what they would do if they were in the same preoperative situation again, 15 (75%) of 20 patients said they would choose the operation again, 3 (15%) of 20 said perhaps, and 2 (10%) of 20 said definitely not. The overall satisfaction score showed a significant improvement in symptoms and patient satisfaction with a decrease from 19.5 ± 2.3 preoperatively to 11.4 ± 1.7 postoperatively ($P = 0.005$).

Of those who were interviewed by telephone (6 patients), none reported a recurrence of rectal prolapse or defecation problems, nor was anyone treated for rectal prolapse elsewhere. Five (83%) of six patients were satisfied with the operative result, but an 81-year-old woman was dissatisfied with her outcome, but could not say why. Thus the ratio of satisfied patients was on the same order of magnitude as in those for whom postoperative follow-up was complete.

Prolapse Recurrence

One patient, a 75-year-old woman, had a recurrence of rectal prolapse 42 months postoperatively, combined with uterine prolapse and a cystocele. She had been very satisfied with the results of her operation for 3½ years until her recurrence, which was sudden. One woman had anterior mucosal prolapse 14 months postoperatively as demonstrated by anoscopy and fluoroscopic defecography. However, she did not have clinical symptoms, and was still very pleased with the outcome of her operation and giving it a rating of 10 points on the patient satisfaction scale. We do not consider this a true recurrence, as mucosal prolapse can be observed by fluoroscopic defecography in healthy, asymptomatic individuals with no clinical relevance.[20,21] In addition, anterior mucosal prolapse rarely develops into complete rectal prolapse.[22] Including the patients who were interviewed by telephone (6 patients, no recurrence reported), our recurrence rate was 1 (3.8%) of 26 patients.

Morbidity

Postoperative morbidity was observed in four patients. One patient reported intermittent perineal pain, which had not been present preoperatively. She was investigated 14 months postoperatively, and a gradual decrease in complaints was observed over time. Overall, she was very pleased with the results of the operation and rated it a 10 on the patient satisfaction scale. One patient had problems with urinary evacuation and impotence, which caused considerable distress but improved over time. He had been operated on for incomplete rectal prolapse with a solitary rectal ulcer, which bled repeatedly and required blood transfusions on several occasions. At follow-up 1 year postoperatively, he still required medical treatment with an α-receptor agonist for urinary evacuation and was successfully using sildenafil (Viagra) for treatment of impotence. At follow-up 2 years postoperatively, he was completely symptom free with regard to rectal prolapse and urinary evacuation, and his sex life had improved. A total of three patients (15%) reported using enemas or laxatives regularly, but only two of them (10%) had problems with stool evacuation. Taken together, prolonged functional problems were encountered in 4 (20%) of 20 patients after laparoscopic rectopexy.

Continence

Thirteen (65%) of 20 patients had at least occasional problems with continence preoperatively, with one patient needing to have a stoma because of incontinence. All of them had problems withholding gas, 11 (55%) of 20 had problems withholding liquid stool, and 5 (25%) of 20 had problems withholding solid stool. Postoperatively, continence was improved in 10 (76%) of 13 patients, but it was slightly worse in two patients (15%) and was unchanged in the patient with the stoma. Five patients observed an im-

Table II. Anorectal manometry pre- and postoperatively in 18 patients with rectal prolapse

	Preoperatively	Postoperatively	*P* value
MAR (mm Hg)	72 ± 8	95 ± 13	0.046
MAS (mm Hg)	105 ± 17	142 ± 19	0.035
Sphincter length (cm)	4.5 ± 0.3	4.6 ± 0.3	0.59
First rectal sensation (ml)	55 ± 9	52 ± 8	0.64
Urge to defecate (ml)	135 ± 13	152 ± 18	0.18
Intolerable volume (ml)	181 ± 16	187 ± 19	0.53
Rectal compliance (ml/mm Hg)	4.5 ± 0.5	3.8 ± 0.6	0.097

MAR = maximum anorectal resting pressure; MAS = maximum anorectal squeeze pressure.
Values are given as mean ± SEM.

provement in the ability to withhold gas, four to withhold liquid stool, and two to withhold solid stool. Of those patients whose continence worsened postoperatively, one reported increased problems withholding gas and liquid stool, and one had difficulty withholding gas, liquid stool, and solid stool (see Table I). The Wexner incontinence score showed a significant improvement postoperatively (6.0 ± 1.0 vs. 3.9 ± 0.8, preoperatively vs. postoperatively, $P = 0.02$).

The patient with the stoma was a 72-year-old woman with rectal prolapse. She had a stoma of the descending colon due to incontinence prior to laparoscopic rectopexy. Inasmuch as her sphincter pressures did not increase postoperatively, and she was satisfied with the stoma, restoration of intestinal continuity was not attempted.

Constipation and Evacuation

Eight patients reported having constipation problems preoperatively, with four patients being occasionally constipated and four being frequently constipated. Two of those with frequent constipation had to use laxatives. Postoperatively 10 patients had constipation problems, with seven of them being constipated occasionally and three being constipated frequently. Of those who were constipated occasionally, five did not have to change their nutritional habits or use laxatives. One patient had to increase her fluid intake and her dietary fiber intake in order to avoid becoming constipated, and one patient used laxatives occasionally. Of the three patients who complained of frequent constipation postoperatively, two had to change their nutritional habits and had to use laxatives regularly, whereas neither was necessary in the third. "Relevant" constipation, requiring either a change in nutritional habits or the use of laxatives, was reported by 4 (20%) of 20, with three of them using laxatives. Three of the 20 patients who had to use laxatives regularly rated 8, 9, and 9.5 points on the patient satisfaction scale, indicating that they were satisfied with their operative results. Taken together, we could not observe a significant increase in constipation problems postoperatively.

Nineteen patients were questioned about evacuation problems; the patient with the stoma could not be evaluated. Nine (47%) of 20 patients reported having evacuation problems preoperatively, compared to 9 of 20 patients postoperatively. Postoperatively, three patients had occasional evacuation problems and four had frequent problems. Two patients had always had evacuation problems and were dissatisfied with the operative result.

Anoscopy and Rigid Sigmoidoscopy

Postoperative anoscopy and rigid sigmoidoscopy showed no proctitis or rectal ulcers. Overt rectal prolapse and mucosal prolapse were observed in one patient each, as described earlier. In 5 of 20 patients there was slight narrowing of the upper rectum, and in 6 of 20 there was distinct narrowing. However, in all cases the rigid sigmoidoscope could be passed through the narrowing, and there was no correlation between evacuation problems or constipation and narrowing of the rectum in our patients.

Anorectal Manometry

Postoperative sphincter manometry showed a significant increase in maximum anal resting and squeeze pressures compared to preoperative measurements (Table II; Figs. 1 and 2). The length of the high-pressure zone, volumes for perception, urge, or pain, and rectal compliance were unchanged (see Table II).

Fluoroscopic Defecography

Preoperative defecography showed an overt rectal prolapse in 10 of 20 patients and an internal rectal

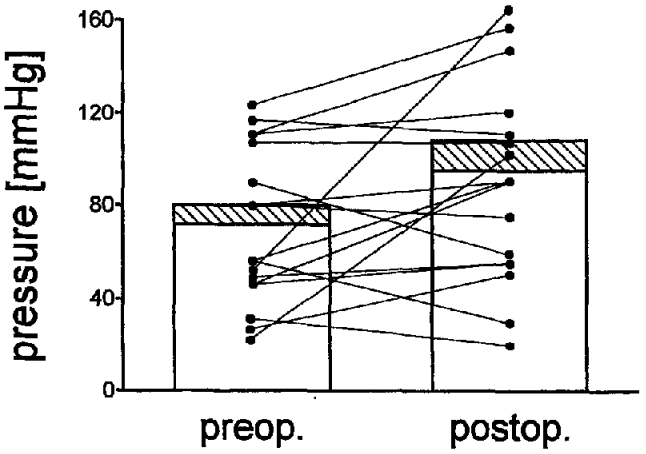

Fig. 1. Maximum anorectal resting pressure in patients with rectal prolapse pre- and postoperatively (n = 17). Values are given as mean *(open bars)* ± SEM *(hatched bars)*. There was a significant increase in maximum anorectal resting pressure postoperatively ($P = 0.046$).

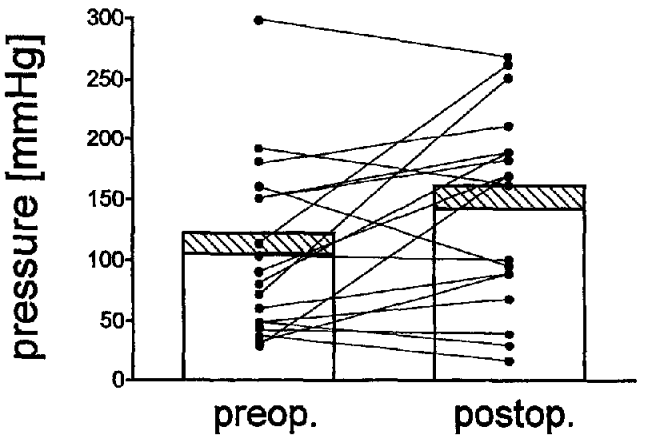

Fig. 2. Maximum anorectal squeeze pressure in patients with rectal prolapse pre- and postoperatively (n = 18). Values are given as mean *(open bars)* ± SEM *(hatched bars)*. There was a significant increase in maximum anorectal squeeze pressure postoperatively ($P = 0.035$).

prolapse in 5 of 20 patients. In one patient, internal rectal prolapse was diagnosed by anoscopy but not by defecography.

The anorectal angle at rest did not change postoperatively (108 ± 4 vs. 112 ± 4 degrees, preoperatively vs. postoperatively, not significant [NS]), and elevation of the pelvic floor during squeezing was unchanged as well (1.7 ± 0.3 vs. 1.6 ± 0.1 cm, preoperatively vs. postoperatively; NS). However, the anorectal angle during defecation was significantly increased postoperatively, and there was a tendency toward decreased pelvic floor descent on straining postoperatively (133 ± 4 vs. 141 ± 3 degrees, preoperatively vs. postoperatively, $P < 0.05$; 2.9 ± 0.3 vs. 2.4 ± 0.4 cm, preoperatively vs. postoperatively, $P = 0.2$; NS).

Rectoceles were judged with respect to size after completed evacuation, the preoperative x-ray films being compared with the postoperative films. In 10 (63%) of 16 patients with rectal prolapse, a concomitant anterior rectocele were observed preoperatively, with two of these (13%) having a diameter of ≥2 cm, a size corresponding to a qualitative score of "severe" and being judged as pathologic.[23] Postoperatively the rectoceles were reduced in size in 9 of 10 patients, with two rectoceles having disappeared completely. The average size was reduced from 1.2 ± 0.4 to 0.8 ± 0.2 cm (± standard error of the mean [SEM], $P = 0.067$), with one of the two pathologic rectoceles being almost absent postoperatively and the other being reduced from 4.8 to 3.3 cm in diameter. However, in one patient who did not have a rectocele preoperatively, a rectocele of 2 cm in diameter was observed postoperatively. The presence of a rectocele did not correlate with evacuation problems postoperatively.

DISCUSSION

Surgical treatment of rectal prolapse can be accomplished by an abdominal or a posterior approach. Of the abdominal approaches, the most frequently applied are the Ripstein procedure, where a circular sling of artificial material is fixed to the sacral promontory and the lateral ligaments of the rectum are preserved, and the Wells procedure, where a semi-

circular trough of artificial material fixes the rectum to the sacral promontory and the lateral ligaments of the rectum are divided. The posterior approaches include the Altemeier and Délorme procedures.[2-5]

There are numerous reports on the functional outcome after open abdominal rectopexy for rectal prolapse.[2-5] In contrast, only a few studies have investigated the functional outcome of laparoscopic rectopexy since its introduction in 1991.[24-29] We evaluated our results after laparoscopic rectopexy and compared them with the results obtained after both open and laparoscopic rectopexy. However, this comparison is hampered by the multitude of operations used to treat rectal prolapse, and to date no randomized comparison between open and laparoscopic rectopexy has been described.

We observed a considerable decrease in symptoms postoperatively. In particular, symptoms related to a sense of prolapse, soiling, pain during defecation, bleeding, and incontinence were absent or at least improved in all patients postoperatively. In a recent study, symptoms were improved in 92% of patients,[28] indicating that as in our study, the great majority of patients will benefit from laparoscopic rectopexy for rectal prolapse.

There are few studies giving a detailed report on patients' long-term satisfaction. In our series, 75% of patients with complete follow-up (20 patients) and 83% of patients interviewed by telephone (6 patients) were satisfied with their operative results, whereas 3 (11%) of 26 patients were dissatisfied. In one study investigating the results after open abdominal rectopexy, 88% of the patients were satisfied with their results, whereas 12% were dissatisfied.[30] This compares well with our results, indicating that approximately 1 in 10 patients will be disappointed with the results of rectopexy. However, in a recent study investigating the outcome after laparoscopic rectopexy, a considerably larger proportion of 38% was disatisfied, mainly because of constipation problems.[29]

We observed a single recurrence, representing a recurrence rate of 3.8%. After laparoscopic rectopexy, several studies reported no recurrences.[25,27-29,31,32] However, at least in some studies, the number of patients was small and the length of follow-up was short. Early recurrence was observed in one small series 1 month after laparoscopic rectopexy.[33] Mucosal prolapse that did not cause any symptoms occurred in one patient in our series as well, and was in the range of the 3% to 25% reported in three laparoscopic series,[26,28,32] which was similar to the 10% to 30% observed after open rectopexy.[30,34,35] To date, although true long-term follow-up studies in patients treated by laparoscopic rectopexy are still lacking, recurrence rates comparable to those observed after open rectopexy can be achieved. The only case of prolapse recurrence that we observed occurred 42 months postoperatively. In one study, after open rectopexy with a mean follow-up of 28 months, the only recurrence of rectal prolapse occurred after 51 months,[35] emphasizing the need for long-term follow-up.

Besides eliminating the symptoms related to protrusion of the rectal wall into the anal canal, rectopexy has also been shown to improve continence and anorectal sphincter function postoperatively. In our series, 65% of patients had continence problems preoperatively. Similarly, in several series on rectopexy for rectal prolapse it was noted that 60% to 70% of patients had some degree of incontinence preoperatively.[30,35-37] There is evidence that a long history of straining and abnormal perineal descent during defecation, as observed in a considerable proportion of patients with rectal prolapse, results in pudendal nerve damage with denervation of the external anal sphincter and the levator ani muscle, altered sphincter and pelvic floor electromyographic activity and, eventually, anorectal sphincter impairment.[38-41] In addition, it has been shown that the extent of pudendal nerve damage in patients with rectal prolapse correlates with the degree of incontinence, and the status of continence can be predicted by measuring pudendal nerve terminal motor latency.[42]

Improvement in anal incontinence was observed in 76% of our patients after laparoscopic rectopexy. Other series have observed improved continence in 64% to 78% of patients after laparoscopic rectopexy,[26-28] which compares well with the 63% (range 46% to 94%) who had improved continence after open rectopexy.[43] In our series, full continence was achieved in 38% of those patients who had reported some degree of incontinence preoperatively. However, only one of five patients who were incontinent for solid stool preoperatively reported being continent for solid stool postoperatively, indicating that patients suffering from severe incontinence derive less benefit from rectopexy with respect to continence. In the laparoscopic studies published to date, postoperative full continence ranged from 0% to 25%.[26,28] In contrast, after open rectopexy, a full continence rate of 36% to 70% of those who were incontinent preoperatively has been reported.[30,35-37,43-46] Possibly laparoscopic rectopexy might be less beneficial with respect to continence compared to open rectopexy. However, as no prospective randomized studies comparing the two techniques have been performed to date, this remains speculative.

Increased continence after rectopexy has been shown to be associated with an improved sphincter electromyogram[47] and increased sphincter presssures in anorectal manometry.[2-4] There is evidence that anal

resting and squeeze pressures are reduced in patients with rectal prolapse compared to an age- and sex-matched healthy control group.[36,41,44] After open rectopexy, an increase in anal sphincter pressures has been observed in most studies,[36,37,43,45,47,48] although not in all,[42,44,49,50] and postoperative continence correlated with preoperative sphincter pressures and postoperative sphincter pressure increases.[43,45] Similar to the results obtained after open rectopexy, we observed a significant increase in anal resting and squeeze pressures after laparoscopic rectopexy. Others have reported a postoperative increase in resting pressure but not in squeeze pressure after laparoscopic rectopexy,[26,51] or no increase in sphincter pressures at all.[27] In our study, all patients were asked whether some form of anal sphincter training was performed before or after rectopexy. Three patients reported receiving sphincter training before surgery, and nine afterward. It is difficult to determine what effect sphincter training had on sphincter manometry, and we cannot rule out the possibility that improved postoperative patient care contributed to increased postoperative sphincter pressures in our study.

Rectal sensitivity is possibly increased in patients with rectal prolapse. One study has shown a reduced maximally tolerable volume in patients with rectal prolapse,[41] although this result has not been duplicated by others.[52] However, these alterations cannot be corrected by rectopexy, since threshold volume, volume for urge, and volume for pain were unchanged postoperatively in our study as well as after open rectopexy.[36,41,44]

In our study, preoperative fluoroscopic defecography showed an anorectal resting angle similar to that in other studies of patients with rectal prolapse or compared to a study population of our own with rectal adenomas.[15,37,43] Compared to a control population, a more obtuse anorectal angle in patients with rectal prolapse has been described.[44] Postoperatively we observed an increased anorectal angle during defecation. Because the rectum is pulled up and fixed to the sacrum by rectopexy, and the pelvic floor descent on straining remains about the same as preoperatively, an increase in the anorectal angle would be expected. However, such changes were not observed after open rectopexy,[44] whereas no data are available for laparoscopic rectopexy.

Postoperative constipation problems are a major concern after rectopexy. There is evidence that a considerable proportion of patients with rectal prolapse are constipated and have a slow colonic transit. Preoperative constipation rates of 19% to 66%* and a prolonged colonic transit time in more than 50% of patients have been reported,[37,54] although rectal evacuation problems and colonic transit time do not correlate directly.[55] Similarly, up to 95% of women with uterovaginal prolapse are constipated, compared to 11% of control women.[56] Obviously pelvic floor disorders and alterations in colonic transit coexist, with the constipation problems possibly being aggravated postoperatively.

We observed constipation problems in 40% of our patients preoperatively, compared to 50% postoperatively. In two studies in which a laparoscopic approach similar to ours was used, postoperative constipation problems were noted in 38% and 40% of patients, respectively.[29,31] In another study of laparoscopic rectopexy, in which the lateral ligaments were left intact and the sigmoid colon was resected, postoperative constipation was observed in only 12% of patients.[28] However, it is difficult to assess the severity of the constipation problems reported in these studies. In our study, although 50% of patients reported being constipated postoperatively, only three had to use laxatives regularly, and we consider our rate of "relevant constipation" which is defined as a change in nutritional habits and/or the need to use laxatives, to be only 20%. Furthermore, all three patients who needed to use laxatives postoperatively were satisfied with their operative results.

The reasons for evacuation and/or constipation problems after rectopexy are still not clear. Division of the lateral ligaments of the rectum has been implicated, since a postoperative increase in constipation problems after rectopexy has been observed.[49,50] In two studies, a reduction in constipation and evacuation problems was observed after preservation of the lateral ligaments.[30,57] However, there are also reports where the lateral ligaments were preserved and the postoperative constipation rate increased from 48% preoperatively to 71% postoperatively,[34] and incomplete emptying and straining were observed in 38% and 31% of patients, respectively.[28] In addition, in a study investigating colonic transit and colonic motility after rectopexy with preservation of the lateral ligaments, increased transit time and reduced colonic motility were observed postoperatively.[52,58] Obviously preservation of the lateral ligaments of the rectum does not necessarily prevent constipation or evacuation problems after rectopexy.

To overcome the constipation problems after rectopexy, a variety of investigators have suggested a concomitant sigmoid colon resection,[37,48,53,58,59] and this approach has also been used laparoscopically.[11,27,28,51] This allows the otherwise increased postoperative colonic transit time to be normalized,[37,58] and thus the constipation problems appear to be significantly re-

*References 30, 34, 37, 48-50, 52, and 53.

duced.[37,49,58,59] However, even after a combination of laparoscopic rectopexy with sigmoid colon resection and preservation of the lateral ligaments, worsening of constipation has been reported in 8% of patients.[28] In addition, if rectopexy is combined with a colonic resection, there is a risk of an anastomotic leak[27] or stricture of the anastomosis,[59] and significant diarrhea may develop[53]; also, the use of an artificial mesh graft in combination with a colonic anastomosis may cause infectious complications. Because a considerable proportion of patients do not report problems with constipation either pre- or postoperatively, resection of the sigmoid colon does not seem justified in all patients. Possibly an individually tailored concept combining rectopexy with resection of the sigmoid colon in those with delayed colonic transit preoperatively might be the best operative choice for patients with rectal prolapse.[48]

In summary, the great majority of patients with rectal prolapse in our study were satisfied with the results of laparoscopic rectopexy. It seems possible to achieve good functional results with laparoscopic rectopexy, but long-term follow-up studies exceeding the time spans investigated thus far are needed to determine the rate of late recurrence. Problems with constipation and rectal evacuation were not resolved by rectopexy in some of our patients. It is possible that combining rectopexy with resection of the sigmoid colon might improve the functional outcome in patients with slow colonic transit.

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Symptomatic Gallstones in Patients With Spinal Cord Injury

Vicky B. Tola, M.D., Stephanie Chamberlain, M.D., Sandra K. Kostyk, M.D., Ph.D., David I. Soybel, M.D.

Patients with spinal cord injury (SCI) have an increased prevalence of cholelithiasis. The goal of this study was to clarify the presentation and management of symptomatic gallstone disease in patients with SCI. We performed a retrospective study of presentation of gallstone complications in patients with SCI who underwent cholecystectomy for complications of gallstone disease. The West Roxbury Veterans Administration Medical Center SCI registry (605 patients) was searched for patients who had undergone cholecystectomy more than 1 year after SCI (35 patients). Gallbladder disease profiles for the 35 patients undergoing cholecystectomy for complications of gallstone disease were prepared, including demographics, clinical presentation, diagnostic studies, operative and pathologic findings, and postoperative complications. All patients were white. Thirty-four were male and the mean age was 50 years (range 35 to 65 years). The majority of patients (66%) complained of right upper quadrant abdominal pain, even those patients with SCI at high (i.e., cervical) levels. Of the 35 patients in our study group, 22 (63%) had biliary colic and chronic cholecystitis, nine (26%) had acute cholecystitis (gangrenous cholecystitis in two), two (6%) had choledocholithiasis symptoms or cholangitis, and two (6%) had gallstone pancreatitis. Major perioperative morbidity occurred in two (6%) of the 35 patients (pulmonary embolus; intraoperative hemorrhage), and there were no deaths. In the great majority of patients with SCI, cholelithiasis presents with chronic pain and not with life-threatening complications. Our findings suggest that presentation is no more acute in patients with SCI than in the general population. Characteristic symptoms and signs are not necessarily obscured by SCI injury, regardless of the level. (J GASTROINTEST SURG 2000;4:642-647.)

KEY WORDS: Biliary tract disease, gallstones, cholecystitis, paraplegia, quadriplegia

It is well recognized that certain subgroups are predisposed to development of gallstones. These subgroups include certain native Americans, women, persons with diabetes, and those who are morbidly obese.[1-5] Among these groups a consensus has emerged regarding the management of gallstones that are detected by imaging studies such as plain x-ray films, ultrasound, or CT scans in the course of an evaluation for unrelated symptoms. For many years it was suggested that asymptomatic gallstones should be removed, especially in groups with a higher-than-normal prevalence of gallstones. This was recommended to reduce the incidence of life-threatening complications such as gangrenous cholecystitis or high levels of morbidity after surgery. Decision analysis, however, has only supported the decision to perform cholecystectomy in symptomatic patients. The use of prophylactic cholecystectomy in any of these subgroups is not recommended.[3-5]

It has been reported that patients with paraplegia or quadriplegia have a higher-than-expected incidence of gallstones.[6-8] However, there is little specific information regarding the likelihood that symptoms or serious or life-threatening complications of gallstones will develop in this subgroup. In addition, it is not known whether the level of neurologic impairment bears any relation to the development of symptoms or complications of gallstones. Since 1990 the Spinal Cord Injury Service at the West Roxbury Veterans Administration Medical Center (VAMC) has been performing abdominal ultrasound examinations in all patients with spinal cord injury (SCI) at 1- to 2-year intervals.

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Table I. Demographics of SCI patients undergoing cholecystectomy

	Total group	Cervical spine	High thoracic spine (>T6)	Lower thoracic and lumbar spine (<T6)
No. of patients	35	18	6	11
Age (mean ± SD)	50 ± 15	47 ± 14	54 ± 15	51 ± 17
No. of males	17 (94%)	6 (100%)	11 (100%)	34 (97%)
No. white	35 (100%)	18 (100%)	6 (100%)	11 (100%)

SD = standard deviation.

In this study we retrospectively used our SCI service database and radiology archives to characterize the crude prevalence of gallstones, symptomatic or asymptomatic, in the SCI population and the proportion of patients with gallstones who develop symptoms or complications requiring surgery. In addition, we compared symptoms and complications of gallstones among SCI cholecystectomy patients with different levels of neurologic impairment. Our data indicate that the prevalence of gallstones is higher than expected but the proportion of these patients who develop symptoms or complications is no different from that expected in the general population. We also found that the incidence of life-threatening complications is low and that the diagnosis of acute cholecystitis is usually not obscured, even in quadriplegic patients.

METHODS

Spinal Cord Injury Database and Record Reviews

The West Roxbury VAMC Spinal Cord Injury Service computerized database was established in 1995 and includes patients who suffered SCI as early as 1945. It contains demographic information, information related to prior hospitalizations and surgeries, and information relevant to SCI and related complications. At the time of this review the registry included 605 patients; 104 were identified as having a history of gallstones or surgery for gallstones or gallstone-related complications (crude prevalence 17%). Of the 104 patients with a candidate history, review of individual records identified 36 patients who had undergone cholecystectomy (cumulative incidence of surgical procedures 34%) at least 1 year after SCI. One of these patients had undergone cholecystectomy as part of a Whipple procedure for carcinoma of the head of the pancreas; the other 35 patients had undergone cholecystectomy for a gallstone-related complication or for acute cholecystitis. The medical records of these 35 patients were reviewed in order to obtain data encompassing the following: demographics, clinical presentation prior to the procedure, studies performed to confirm diagnoses, operative findings, pathologic findings, and postoperative complications. Discharge summaries, operative notes, and pathology reports were reviewed for each patient to confirm and extend the information contained in the database.

RESULTS

Study Population

Mean age was 50 years (range 35 to 65 years). All patients were white and all but one patient was male (Table I). All patients suffered SCI from traumatic causes. SCI was complete in 57% and incomplete in 43%. At the time of surgery, the prevalence of diabetes was 14% and 14% had a history of hepatitis. One patient had documented cirrhosis at the time of cholecystectomy. The prevalence of these conditions is similar to that in patients without gallstones in SCI registries here and elsewhere.[10]

Fig. 1 summarizes, among the 35 cholecystectomy patients, how many had been injured at the cervical level (C2 to C8), the high thoracic level (T1 to T7), and the low thoracic-lumbar level (T8 and below). This was compared to the distribution of injury levels among the entire group of 605 patients in our SCI database at the West Roxbury VAMC. In the entire group of patients with SCI, 52% were quadriplegic, 30% were "high thoracic" paraplegics, and approximately 18% were "low thoracolumbar" paraplegics. The distribution of SCI levels was no different in the cholecystectomy group than in the population as a whole (chi-square test), suggesting that symptomatic gallstones are not associated with any one region of myelopathy.

Table II summarizes the presenting symptoms of these 35 patients categorized according to the level of SCI. Most patients (66%) complained of right upper quadrant abdominal pain, regardless of the SCI level. Referred shoulder pain was present in one third of patients. Nausea/emesis was present in almost half. Three patients (9%) presented with jaundice. The clinical presentation was not very different among the groups with different SCI levels.

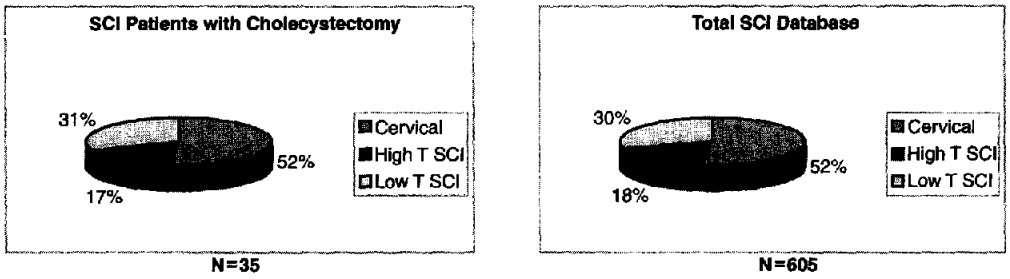

Fig. 1. Comparison of injury levels in SCI patients who underwent cholecystectomy and patients in the total SCI database. T = thoracic.

Table II. Clinical presentation of patients with spinal cord injury undergoing cholecystectomy

Symptoms/signs	Total group	Cervical spine	High thoracic spine	Low thoracolumbar spine
No. of patients	35 (100%)	18	6	11
Right upper quadrant pain	23 (66%)	13	3	7
Shoulder pain	11 (31%)	5	2	4
Diffuse/vague	14 (40%)	7	3	4
Fever (>100° F)	16 (46%)	9	3	4
Nausea/emesis	17 (49%)	8	3	6
Hypotension	2 (6%)	1	1	0
Jaundice	3 (9%)	2	0	1
Rebound	5 (14%)	2	1	2
Guarding	7 (20%)	3	0	4
Malaise/weight loss	10 (29%)	4	3	3

Table III. Laboratory findings at presentation for patients with spinal cord injury undergoing cholecystectomy

	Acute cholecystitis	Chronic cholecystitis	Acute pancreatitis	Common bile duct stone
No. of patients	9	22	2	2
White blood cell count (mm^3)	16.7 ± 8.0	8.5 ± 3.5	7.8 ± 0.7	7.1 ± 4.2
Serum alkaline phosphatase (IU/dl)	173 ± 105	94 ± 36	455 ± 171	277 ± 168
Serum total bilirubin (mg/dl)	2.6 ± 3.5	0.6 ± 0.3	2.8 ± 3.2	13.1 ± 8.8
Serum amylase (IU/dl)	118 ± 145	76 ± 76	619 ± 503	87 ± 69

Results reported as mean ± standard deviation.

Based on clinical history and findings, and laboratory data, patients were classified into the following four groups: those presenting with acute cholecystitis, those presenting with biliary colic and chronic cholecystitis, those presenting with choledocholithiasis (with or without cholangitis), and those presenting with acute pancreatitis. Table III summarizes the laboratory findings at the time of presentation grouped according to the clinical syndrome. Thus acute cholecystitis was the clinical diagnosis in nine patients (26%), chronic cholecystitis in 22 (63%), gallstone pancreatitis in two (6%), and choledocholithiasis in two (6%). White blood cell counts were elevated, as expected, in patients with acute cholecystitis (16.7 ± 8.2). The mean of the total bilirubin levels for the group with acute cholecystitis was also elevated (2.6 ± 3.5 mg/dl) but skewed by one patient who developed acute cholecystitis after being admitted in cardiac arrest; without this patient the mean was 1.6 ± 2.6 mg/dl. The patients with chronic cholecystitis had laboratory values that were generally within normal limits. As expected, the group with gallstone pancreatitis had elevated levels of serum amylase. As expected in a group with choledocholithiasis, the mean total serum bilirubin level was elevated at 13 ± 9 mg/dl.

Prior to May of 1993, all procedures were performed as open cholecystectomies. Since that time, 15 cholecystectomies have been performed after the in-

Table IV. Operative findings in patients with spinal cord injury undergoing cholecystectomy

Operative findings	Total group	Cervical spine	High thoracic spine	Low thoracolumbar spine
No. of patients	35 (100%)	18	6	11
Perforation	0 (0%)	0	0	0
Wall ischemia	2 (6%)	1	0	1
Inflammation (acute or chronic)	29 (83%)	17	4	8
CBD dilated	3 (9%)	1	0	2
CBD stone	2 (6%)	1	0	1
Stones in gallbladder	32 (91%)	17	5	10
Multiple	24 (69%)	10	4	9
Single	8 (23%)	7	1	1
None	2 (6%)	1	1	2
Not recorded	1 (3%)	0	0	1

CBD = common bile duct.

Table V. Perioperative complications in patients with spinal cord injury undergoing cholecystectomy

Complications	Total group	Cervical spine	High thoracic spine	Low thoracolumbar spine
No. of patients	35 (100%)	18	6	11
Major intraoperative	1 (3%)	0	0	1
Hemorrhage	1 (3%)	0	0	1
Major postoperative	1 (3%)	1	0	0
Pulmonary embolus	1 (3%)	1	0	0
Minor intraoperative	1 (3%)	0	0	1
Hemorrhage	1 (3%)	0	0	1
Minor postoperative	12 (34%)	7	1	4
Lung infiltrate	1 (3%)	1	0	0
Fever	5 (14%)	2	0	3
Ileus <48 hr	4 (11%)	3	0	1
High serum amylase	2 (6%)	2	0	0
Wound hematoma	1 (3%)	0	1	0
Urinary tract infection	2 (6%)	0	0	2

troduction of laparoscopic procedures at the West Roxbury VAMC. Three of these 15 cholecystectomies were not attempted laparoscopically; for two patients early in our experience, the procedure was considered too risky. In the other patient, an open common bile duct exploration was required for removal of an endoscopically placed stone basket that had become trapped in the common bile duct. Of the 12 patients in whom the procedure was initiated laparoscopically, one was converted to an open procedure because of an unclear anatomy and the other was converted because of uncontrolled bleeding. In the total group of 35 patients, 23 (66%) had open cholecystectomies, two (6%) were converted to open procedures, and 10 (28%) had their procedures completed laparoscopically. Intraoperative cholangiography was performed in 23% of the patients to verify anatomy or to verify the absence of a common bile duct stone.

The operative and pathologic findings are summarized in Table IV. At the time of operation, the majority of patients (88.6%) had stones in the gallbladder. Twenty-three patients had multiple stones and nine had single stones documented. No gallbladder stones were found in two patients. Two patients with acute cholecystitis had no stones in the gallbladder or biliary tree. One patient did not have any stone information recorded by the surgeon or pathologist.

Among 31 patients with documented pathologic examination of specimens, none had a perforated gallbladder. Two patients (6%) had evidence of transmural ischemia. Seven other patients had findings of acute inflammation, consistent with their presentation of clinically acute cholecystitis. The other 22 patients had evidence of chronic inflammation mixed variably with evidence of acute inflammation.

Table V summarizes perioperative events in our study group. Major complications occurred in two patients. Minor postoperative complication rates were similar in the group with acute cholecystitis (3 [33%] of 9) and the group with chronic biliary colic (7 [32%]

of 22). There were no deaths. A number of patients had more than one complication; one patient with pulmonary embolus also had mild postoperative pancreatitis, two patients had both urinary tract infection and fever, and one patient had both ileus and mild postoperative pancreatitis. In the two patients with postoperative pancreatitis, there were compounding factors. One patient developed pancreatitis, most likely as a result of preoperative endoscopic retrograde cholangiopancreatography to investigate the ultrasonic finding of an enlarged common bile duct, and the other patient developed pancreatitis, most likely as a complication of the low-flow state created by the cardiac arrest for which he was admitted. Overall, 23 (66%) of the 35 patients had no complications in the postoperative period.

DISCUSSION

In this survey the prevalence of gallstones in this population was 17%. The overall prevalence of complications attributable to gallstones, in those patients who had evidence of gallstones, was between 30% and 35%. The likelihood of life-threatening complications of gallstones (such as gangrenous cholecystitis, necrotizing pancreatitis, or cholangitis) was very low. Moreover, serious morbidity and mortality following the operation, even when performed urgently or semiurgently, were acceptable. One other series of patients with SCI has been reported that is equivalent in scope to that reported here. In that study, by Moonka et al.,[9] the overall prevalence of gallstones was 31%, which is somewhat higher than that reported in the smaller series.[6-8] However, their study had the advantage, as in the current study, of following patients with routine abdominal ultrasound. Also, Moonka et al.[10] found, as we have here, that the incidence of complications or symptoms leading to cholecystectomy is approximately 30%. Likewise, they observed that the likelihood of life-threatening complications was low. Our findings confirm and extend those of Moonka et al.[9,10] by emphasizing that acute and chronic symptoms are not necessarily obscured by the presence of high-level SCI. Taken together, their results and our findings indicate that, although SCI predisposes patients to gallstone formation, such stones do not present with uncharacteristic clinical syndromes or aggressive complications.

The prevalence of gallstones in middle-aged men has been characterized in a number of studies[1,11] and seems to vary from 2% in young men (age 30 or under) to 15% in those aged 70 and over. With the use of crude and imprecise historical data, we found that the prevalence of gallstones (17%) is somewhat higher than that expected for a group of men of mixed ages. These findings generally confirm the original observation made by Apstein et al.[6] from our institution. In that study our colleagues used a comparison group of age- and sex-matched persons who had died and undergone autopsy. We do not purport to have a similar control group and our estimate of gallstone prevalence is rendered uncertain by a lack of reliable documentation to corroborate information reported in patient histories. Nevertheless, it seems clear that the incidence of gallstones in patients with SCI is increased compared to that expected in a middle-aged male population.

The likelihood that asymptomatic stones would ultimately become symptomatic is difficult to assess, except in a program of systematic follow-up. In the long-term study by Gracie and Ransohoff,[12] the cumulative probability of developing symptoms or complications was 10% at 5 years and 18% at 25 years after diagnosis. Although that study has frequently been criticized because it included essentially only white males, it may represent a more appropriate comparison group for our patients than other studies that include women and more diverse ethnicity. Other studies consisting of more heterogeneous groups also report that asymptomatic stones are likely to become symptomatic at a rate of approximately 2% to 3% per year for the first 10 years after diagnosis; thereafter the likelihood of developing symptoms is not known with any confidence.[13]

Although we are currently initiating such a program, we cannot address this issue directly in the context of the current study. Of note, we were not able to identify patients in the database who were symptomatic, but who did not undergo operation. In keeping with the recommendations of Apstein et al.,[6] our policy has been to perform cholecystectomy in those patients whose symptoms, signs, and confirming imaging data made the diagnosis of symptomatic disease likely. We have not recommended cholecystectomy when gallstones were identified in patients who were thought to be asymptomatic.

Three additional issues are raised by our findings. The first is the nature of the symptoms experienced by SCI patients with gallstones. Because patients with SCI experience altered somatic sensation,[14,15] we anticipated that such patients might not experience the pain or tenderness typical of patients with colic or even localized peritonitis. Our review indicates that SCI patients with complications of gallstone disease have clinical presentations not so dissimilar from the general population. Among the nine patients who presented with or developed acute cholecystitis while under observation, most had rebound tenderness or involuntary guarding, in addition to progression of symptoms or elevation of the white blood cell count.

Ultrasound was generally accurate in identifying patients with acutely inflamed gallbladders. These findings are in agreement with previously reported data from the smaller series of patients.[16]

A second issue involves the suitability of such patients for laparoscopic approaches. In our series of patients, 15 had cholecystectomy performed after the introduction of laparoscopic cholecystectomy to our facility. Of the 12 patients thought to be suitable for laparoscopy, two (16%) required conversion to open cholecystectomy. Although the numbers are small and reflect, in part, the early evolution of the institution's experience with laparoscopy, we believe they support the contention that spinal cord injury does not present a contraindication to a laparoscopic approach.

The third issue involves the suitability of the SCI population for urgent and elective abdominal surgery. Most of our patients were not acutely ill and therefore not potentially at high risk for postoperative morbidity/mortality. In fact, our rates of postoperative complications seem acceptable, in view of the generally older nature of the population and the comorbidity that usually accompanies long-standing SCI. Because our patients did not present with advanced illness and did not have significant major morbidity after surgery, our data suggest that SCI patients with symptomatic gallstones may be evaluated and managed using indices of clinical suspicion and diagnostic approaches similar to those used for nonmyelopathic individuals. Our data thus do not support a policy recommending cholecystectomy for asymptomatic stones in the SCI population.

CONCLUSION

This retrospective review of a moderate-sized SCI patient population reveals the following: (1) cholelithiasis is more prevalent in the SCI population than in the general population; (2) SCI patients with gallstones are not at increased risk of morbidity/mortality; and (3) the clinical presentation of SCI patients with gallstones is not so different compared to the general population, and this is not influenced by the level of spinal cord injury. We conclude that patients with symptomatic gallstones can undergo evaluation and management protocols similar to those practiced for patients without myelopathy. In addition, our observations indicate that there is not likely to be a benefit from prophylactic cholecystectomy in SCI patients with asymptomatic gallstones.

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Letters to the Editors

Isolated Right Segmental Hepatic Duct Injury: A Diagnostic and Therapeutic Challenge

To the Editors:

I read with interest the excellent article by Lillemoe et al.[1] on postoperative diagnosis and management of injury to the right segmental hepatic duct. I would like to ask the authors of this article whether, based on review of their nine referred cases, and from their extensive experience with biliary surgery in general, they can point out the most vulnerable anatomic location of these ducts to injury at laparoscopic cholecystectomy. Does the injury occur at the triangle of Calot when one dissects too medially close to the common hepatic duct, or does it occur when one dissects away the proximal part of the gallbladder (infundibulum) from the liver, after the cystic duct and artery have been clipped and severed? In some patients the proximal portion of the gallbladder is closely adherent to the right side of the porta hepatis. A segmental duct that drains into the common hepatic duct, rather than into the cystic duct, should be more prone to injury when dissecting away the gallbladder from the liver, which in laparoscopic cholecystectomy is carried out with electrocautery. In the figures presented in their article,[1] only one to four clips are seen in the gallbladder region, meaning that either the aberrant ducts had been cut without having been seen or they had been damaged by some other mechanism such as electrocautery.

Cyrus Vakili, M.D.
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REFERENCE

1. Lillemoe KD, Petrofski JA, Choti MA, Venbrux AC, Cameron JL. Isolated right segmental hepatic duct injury: A diagnostic and therapeutic challenge. J GASTROINTEST SURG 2000:4:168-177.

Reply

Dr. Vakili has brought up an important point concerning our report on isolated right segmental hepatic duct injuries—that is, how to avoid these injuries. There are numerous anatomic variations of the "normal" biliary anatomy. Therefore the exact mechanism of how a duct may be injured can vary from one person to another. However, generally when injured, the right posterior segmental hepatic duct joins the common hepatic duct low and posteriorly. It is most likely that the cystic duct and cystic artery have already been dissected and clipped (as noted by Dr. Vakili in the figures in our paper), which then allows the surgeon to relax and begin dissecting the infundibulum of the gallbladder away from the liver. It is during this dissection, which can sometimes extend somewhat posteriorly, that these ducts are most likely injured. Dr. Vakili correctly notes that the close proximity of the gallbladder infundibulum to the porta might lead to these injuries without recognition while the surgeon believes that the procedure is progressing in a satisfactory fashion. In cases in which the cautery is used for dissection, the duct is divided leading ultimately to a bile leak. If clips are applied, it is likely that no leak will occur and the "injury" will go unrecognized. Most of these cases will probably result in atrophy of the liver segment without any long-term sequelae. It is possible that the true incidence of these injuries is in reality much higher than currently appreciated.

In conclusion, although there are many other variations of the biliary anatomy, such as the right posterior segmental duct inserting into the cystic duct, we believe that based on the observations in these nine patients, as well as in other patients undergoing biliary tract surgery at our institution, the preceding is the most common scenario. We thank Dr. Vakili for his letter, and for directing the focus toward avoidance of such injuries—which of course is key to the performance of a successful laparoscopic cholecystectomy.

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1. Lillemoe KD, Petrofski JA, Choti MA, Venbrux AC, Cameron JL. Isolated right segmental hepatic duct injury: A diagnostic and therapeutic challenge. J GASTROINTEST SURG 2000:4:168-177.

Reply

Dr. Vakili has brought up an important point concerning our report on isolated right segmental hepatic duct injuries—that is, how to avoid these injuries. There are numerous anatomic variations of the "normal" biliary anatomy. Therefore the exact mechanism of how a duct may be injured can vary from one person to another. However, generally when injured, the right posterior segmental hepatic duct joins the common hepatic duct low and posteriorly. It is most likely that the cystic duct and cystic artery have already been dissected and clipped (as noted by Dr. Vakili in the figures in our paper), which then allows the surgeon to relax and begin dissecting the infundibulum of the gallbladder away from the liver. It is during this dissection, which can sometimes extend somewhat posteriorly, that these ducts are most likely injured. Dr. Vakili correctly notes that the close proximity of the gallbladder infundibulum to the porta might lead to these injuries without recognition while the surgeon believes that the procedure is progressing in a satisfactory fashion. In cases in which the cautery is used for dissection, the duct is divided leading ultimately to a bile leak. If clips are applied, it is likely that no leak will occur and the "injury" will go unrecognized. Most of these cases will probably result in atrophy of the liver segment without any long-term sequelae. It is possible that the true incidence of these injuries is in reality much higher than currently appreciated.

In conclusion, although there are many other variations of the biliary anatomy, such as the right posterior segmental duct inserting into the cystic duct, we believe that based on the observations in these nine patients, as well as in other patients undergoing biliary tract surgery at our institution, the preceding is the most common scenario. We thank Dr. Vakili for his letter, and for directing the focus toward avoidance of such injuries—which of course is key to the performance of a successful laparoscopic cholecystectomy.

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Prospective Randomized Trial of Early Initiation and Hospital Discharge on a Liquid Diet Following Elective Intestinal Surgery

To the Editors:

I read with great interest the article by Behrns et al.[1] concerning liquid diet and early postoperative discharge after intestinal surgery. I simply cannot believe that sending patients home on a liquid diet and decreasing the length of the hospital stay would fail to decrease hospital costs. Is there a fallacy in that conclusion?

I must also point out that a clear liquid diet, which is basically jello, broth, and some other liquid, does not provide enough nourishment for persons who are recovering from a major operation. For many years I have used Vivonex, which provides approximately 1 calorie/ml, for all postoperative gastrointestinal patients, and a brief report has been published.[2]

The succus entericus puts out 8 to 10 liters per day and a diet will not be harmful to patients. The offending factor is swallowed air, as was shown many years ago by Gerber.[3] Vivonex, when administered through a feeding tube, is well tolerated. It is begun on the day of the operation, it can be increased rapidly, and by the third or fourth postoperative day, patients are able to be discharged, most with no untoward effects.

We have used our method in more than 100 cases and have not seen any complications from its use. There are some patients who cannot be fed the day of the operation, but certainly by 24 hours postoperatively the feeding is begun in all patients. Waiting for bowel sounds is not necessary and bowel function resumes in the hospital or at home after the patient is discharged. The number of days spent in the hospital and the hospital costs are decreased.

We therefore suggest that instead of giving patients liquids by mouth, they be given a nourishing diet through a feeding tube, preferably one that is placed in the duodenum during the operation. There are other types of feedings besides Vivonex, but we like Vivonex because it does not have to be diluted and it provides a high caloric concentration for persons who need these calories to recover.

Fernando Ugarte, M.D.
Community Physicians Clinic, Inc.
Marysville, Kansas

REFERENCES

1. Behrns KE, Kircher AP, Galanko JA, et al. Prospective randomized trial of early initiation and hospital discharge on a liquid diet following elective intestinal surgery. J GASTROINTEST SURG 2000;2:217-221.
2. Ugarte F. Letter to the Editor. Am Surg 1999;63:565-566.
3. Gerber A. Gastrointestinal distension in infants. J Pediatr 1955;46:66-77.

Reply

We appreciate Dr. Ugarte's interest in and comments on our article. Intuitively, because length of hospital stay is the major determinant of hospital costs, cost analysis between patients discharged on a standard diet versus a liquid diet should favor patients dismissed sooner on a liquid diet. Cost analysis, however, is multifactorial, and miscellaneous costs may make this difference inapparent in this relatively small study.

We agree that a clear liquid diet provides few calories and amino acids for tissue repair after a major operation, but not all patients require full nutrition in the postoperative period.[1] Our intent was not to provide full nutrition in the early postoperative period to patients undergoing elective gastrointestinal surgery, but to administer adequate fluid intake that would allow earlier dismissal from the hospital with resumption of a regular diet in the home environment.

Furthermore, enteral feeding of *all* patients following gastrointestinal surgery has several disadvantages. First, all patients require enteral access such as a nasoduodenal, nasojejunal, or jejunostomy tube. Placement and maintenance of these tubes are associated with a small but definite morbidity. Patient discomfort may not be insignificant. Moreover, the costs associated with sending a patient home on enteral feeding may be substantial. For instance, at the University of North Carolina, initiation costs for home administration of Vivonex are at least $75 per day. Also, many third-party payers will only reimburse enteral nutrition when it is the sole source of caloric intake. Thus many patients must bear this expense. Finally, administration of this elemental diet has not been proved to decrease the length of the hospital stay or costs in a prospective, randomized trial.[2]

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Amanda Kircher, R.N.
Mark J. Koruda, M.D.
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REFERENCES

1. Torosian MH. Perioperative nutrition support for patients undergoing gastrointestinal surgery: Critical analysis and recommendations. World J Surg 1999;23:565-569.
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Journal of
Gastrointestinal Surgery

Multivariate Analysis of Factors Predicting Outcome After Laparoscopic Nissen Fundoplication

To the Editors:

I read with great interest the article by Campos et al. (J GASTROINTEST SURG 1999;3:292-300) and found it to be an excellent article evaluating objective parameters. There is one point, however, that should be approached with caution before definite conclusions are drawn—that is, the short follow-up of a mean of 15 months. At this time patients with Barrett's esophagus who undergo classic open surgery show a 90% rate of good or excellent responses. However, at 8 or 10 years we have noted a recurrence rate of 60%.[1] It is very important to have a longer follow-up of these patients to determine their late response. Therefore, the results of the present paper should be as follows: 173 patients had an excellent or good outcome (87%) and 26 (13%) showed a fair or poor outcome at a mean of 15 months' follow-up. It is not known what will happen 5 years later, but it is possible that the percentage of patients with a fair or poor outcome will rise.

Prof. Dr. Attila Csendes, F.A.C.S.
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REFERENCE

1. Csendes A, Braghetto I, Burdiles P, Puente G, Korn O, Díaz JC, Maluenda F. Long-term results of classic antireflux surgery in 152 patients with Barrett's esophagus: Clinical, radiologic, endoscopic, manometric, and acid reflux test analysis before and late after operation. Surgery 1998;123:645-657.

Reply

We thank Dr. Csendes for his interest in our report. He points out that the follow-up was relatively short, which is true. Longer term analyses including 5-year studies are presently emerging.

Dr. Csendes recently reported symptomatic success in 50% to 60% of patients with Barrett's esophagus at 10 to 11 years. This brings up the question of why Barrett's esophagus was not identified as a predictor of outcome in our multivariate analysis. There are two likely reasons for this. The first, as he pointed out, may be the relatively short follow-up. We believe, however, that more important is the fact that our center advocates the liberal use of transthoracic antireflux procedures, particularly in patients with Barrett's esophagus. Thus the type of procedure selected may play a significant role. The discussion of our report points out that this multivariate analysis was carried out only in patients **selected** for laparoscopic fundoplication. This encompasses approximately 80% of those who undergo primary antireflux surgery at the University of Southern California. A disproportionate number of patients with Barrett's esophagus are approached via thoracotomy, which allows more complete esophageal mobilization, and we believe a better long-term symptomatic outcome.

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