2005 SSAT Presidential Address: Heroes, Mentors, and Teammates

Keith D. Lillemoe, M.D.

The culmination of the presidency of most surgical organizations is the opportunity to give a presidential address. I have chosen "Heroes, Mentors, and Teammates" for the title of this address. If this seems strange to you, you maybe don't know me very well. Throughout my life from childhood to the present, my love of sports has been an ever-present influence on me and those around me. In my mind, surgery is no different from sports. It is a form of competition, and although wins and losses are not published as the standings in the newspaper, and hits, errors, near misses, and slam dunks may not show up on Sports Center, those of us in the practice of surgery, and particularly alimentary tract surgery, encounter them on a daily basis. Surgery is also the ultimate team sport, with staff, residents, nurses, and other professionals working together. The competition is the disease, or even in some cases, the patient and the problems that they encounter. In many cases, victory does not come easy, and losses, just as in sports, can bring a tear to the eye of the competitor.

Although the address is not about sports, I will use sports and sports analogies to assist me throughout; specifically, as I pay a tribute to those who have contributed to my professional career and my many heroes of the SSAT. This talk also offers a challenge to the society. We, as a society, are at a crossroads with the opportunity for either success or failure. One of the areas of opportunity is to impact surgical training, to participate in a system that not only trains surgical residents in the basics of GI, foregut, or HPB surgery, but to go beyond this to a new level of training of true specialists in complex GI surgery to mentor those individuals who will lead the advancement of our field for generations to come.

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These opportunities and challenges will not come easy. We as a society must identify partners or teammates to help us best develop a system that will endure, particularly at this time of significant change in traditional surgery training.

Finally, although we need to focus on training of GI specialists of the future, we cannot lose sight of our most important society resource, our rank and file membership. It is time that we, as a society, look carefully at what we offer to our membership both now, and more importantly, how we can better serve them in the future. Can we do this alone, or perhaps are there opportunities to again work with both our existing and future teammates to solve these problems?

HEROES

Just like in sports, surgeons have heroes. In some cases, these heroes may be the giants of their field,

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but more often, heroes are those individuals who, through their personal contributions, have had a direct positive effect on our careers. I have been fortunate throughout my career to not only have great surgical heroes, but the opportunity to work in cities with sports heroes of significant magnitude. My time in Baltimore encompassed Cal Ripken's entire career and certainly I still get goose bumps thinking of the night when he broke the consecutive game record of Lou Gehrig. Although some may not look as fondly upon Ray Lewis as those of us who cheered on the Ravens to the Super Bowl a few years back, I think you would be hard-pressed to find an inspirational leader who leads by example more than Ray Lewis during his career in Baltimore.

My move to Indianapolis has provided me the opportunity to adopt two other heroes who are remarkable both in their performance and in their personal attributes. The surgical precision of Peyton Manning in dissecting the opponent's defense is unsurpassed as a quarterback. Finally, to be able to witness Reggie Miller, particularly in this year of such conflict on his team, rise to such a high level in the final year of his career and lead the Pacers into the second round of the NBA playoffs is certainly a remarkable feat. Thinking of these four individuals, I see qualities that we, as surgeons, can appreciate. The dependability of Ripken, the inspirational leadership of Lewis, the precision of Manning, and the ability of Miller to step up for his team at a time of adversity are qualities we all admire in our surgical heroes. A notable fact is also that, in this time of significant player movement in all of professional sports, all four have played their entire career with one team.

Finally, I can't mention sports heroes without mention of my beloved Yankees, and specifically those great teams of the late 1990s. Those teams were not made up of high-priced superstars, but rather team players, many homegrown, who felt that the success of the team was far more important than that of the individual. I would contend this is a great formula for a surgical department.

It is the tradition of any presidential address to acknowledge and thank publicly those individuals who have been important in the individual's career. In my mind, these are my ultimate heroes, the people who, through their leadership, their guidance, their support, have provided me with the opportunity to achieve what little significance I have had thus far in my career.

Being at Johns Hopkins as a student and resident, I had many heroes on the house staff and faculty: Mike Zinner, Greg Bulkley, Russ Posteir, and James Sitzmann were among the senior residents who stimulated me to a career in academic gastrointestinal surgery. But perhaps the individual who had the greatest influence upon me early in the course and brought me to my first SSAT meeting was not at Hopkins, at least at that time. John Harmon was the individual who introduced me to basic science research at the Walter Reed Army Institute of Research. John Harmon is indeed a hero and certainly deserves recognition for the fact that both the president, and the president-elect of this organization, Barbara Bass, got their start in academic surgery under his direction.

A second academic hero was Henry Pitt. Henry had been my chief resident when I was an intern, and then assumed his first faculty appointment at UCLA. I was fortunate that when Henry returned to Hopkins from UCLA, I was given the opportunity to work under his guidance in both the clinical and basic science arena. Henry is certainly a hero in his role as a mentor. I know of no one else who does such a good job of putting people into the position to be successful and then standing behind them as they reach their goals. I am now fortunate again to have him with me at Indiana.

I spent 28 years at Johns Hopkins, and I must say for at least for 25 of them I had the opportunity to work side-by-side with a person who has really become my best friend. Charles Yeo certainly has been a hero in my eyes in terms of his leadership, his technical ability, and his high level of competitiveness, both on and off the athletic field, in and out of the operating room, and in helping to build the outstanding pancreatic cancer program at Hopkins. We were a constant stimulus to each other, ever pushing the other to the next level. All this and remaining the best of friends.

Without a doubt, however, my most significant hero throughout my academic career has been Dr. John Cameron. Dr. Cameron, after I finished my training at Johns Hopkins, kept me on as a junior faculty member and provided a great opportunity for a young faculty member with an interest in GI surgery to succeed. The history of Johns Hopkins is filled with great "schools of surgery." The residents who finished under Dr. Halsted, and who went on to be pioneers in the development of surgical training and the practice of safe and meticulous surgery, provided the basis upon which most training programs in this country have been built for over a century. Certainly, Dr. Alfred Blalock's school of cardiac surgeons, which produced such surgeons as Spencer, Bahnson, Cooley, and Sabiston, is among the greatest in history and certainly led to the advancement of cardiovascular surgery as a specialty, but I am confident that the Cameron school of GI

surgery and what was accomplished during those years under his leadership will certainly go down as equal to the others in terms of the contributions.

Although it may seem strange, perhaps my greatest heroes over the last decade in Baltimore have been the Hopkins surgical residents. Their constant stimulation to me as a faculty member to be the best in their eyes, as well as their contributions to our department's accomplishments, is certainly a source of great pride for me. These young men and women were the best, and it was certainly a pleasure to have the opportunity to participate in their training. I expect great things from many in the future. My list of heroes has now expanded to include the faculty and house staff that I have inherited and recruited over the last two years at Indiana University. We are developing an outstanding group, particularly in GI and general surgery. I appreciate their acceptance of me and my passion to create something special at this institution.

Finally, my ultimate heroes are my family. My parents, my wife Cheryl, and our four children, Chris, Shannon, Becky and Heather, who have accepted the fact that their father had many responsibilities, some of which took me away from important things in their lives. A great surgeon once said, "Your kids don't read your CV," but certainly my family knows how to make one believe that they are important and to be there to support you when you really need them.

My list of heroes doesn't end here. I think it important to acknowledge that the SSAT has heroes amongst the organization. Clearly one could go back to the founders of the organization and subsequent leaders of American surgery that have served as presidents of the society: Zollinger, Welsh, Rhoads, Warren, Longmire, Moody, Thompson, Jones, Polk, Jaffe, Silen, and many others who did so much to create such a great organization, but I would like to acknowledge my personal heroes in the society. Those are the individuals who have played such an important role over the last decade or so, during which time I have been actively involved in the society. These are the individuals who make this society the premier GI surgical society in the world.

First, Bernard Langer in 1993 set an agenda for the society, including expansion of membership, initiating our own journal, and fostering advanced training in GI surgery. Long before anyone else, Dr. Langer initiated an advanced HPB fellowship, which continues to be the gold standard for the training in this specialty. He must be proud to see how the society has accomplished these goals. Keith Kelly, who, along with Dr. Cameron, have not only served as presidents, but are the founding editors of our great *Journal of Gastrointestinal Surgery*. Without their hard work, this valuable and highly visible product of our society would never have reached the level of success that it has in just a few short years. Larry Way picked up the call of Dr. Langer with pursuit of advanced GI training and personally led the membership charge to bring this organization to the size where we were able to have the opportunity to establish the journal and offer more to our membership. This could not have succeeded without the very capable chair of the membership committee at that time, Bob Beart, who is still serving as the chairman of the board of trustees. Tom Demeester served as president of the society for two years due to the tragic death of John Ranson. Tom continued the growth of the society to new heights and was instrumental in the actual founding of the journal. David Fromm and Bing Rikkers, who like me, served as secretaries of the society and continued onto the presidency. They both served the organization at times of substantial growth and expansion of activities for the membership.

Andy Warshaw, who despite his strong academic surgery background, increased the opportunities for community-based surgeons in the organization and had the insight to open the doors for cooperation of our society with international GI surgical groups.

Mike Sarr, one of my old Hopkins' heroes, was the first to serve five years as Program Committee chairman that lead the expansion and integration of the SSAT program within DDW. Mike also currently serves the society as President of the SSAT Foundation. Joe Fischer has been the financial backbone of the society for a number of years and has taken a big step forward in personally strengthening our foundation. Finally, Carlos Pellegrini, who put into action the steps to begin the development of advanced GI surgical fellowships with the formation of a tripartite society task force, and who still, in a nonparochial fashion, serves so well as the leader of the Digestive Disease Week Council.

There is also a bright leadership in the future. The next President, Barbara Bass, is clearly one of the most prominent and influential leaders of American surgery. Barbara is past chairperson of the American College of Surgeons Board of Governors and currently a member of the Board of Regents of the College. She is currently chairperson of the American Board of Surgery. She has already impacted this organization significantly as program committee chair. It is a great honor for the society to have Barbara as our first woman President, and I can't imagine anyone better suited. Bill Traverso is a person who has contributed greatly to this society with little recognition. Bill has given

unselfishly of his time as recorder for the last five years, insuring that our quality papers from the meeting reach publication in our journal in a timely fashion. He has also served as the chairman of the Publication Committee and led to the development of the SSAT Web site and our practice guidelines.

Others such as Dave McFadden, Jeff Matthews, Dave Rattner, Jeff Peters, Mark Callery, Yuman Fong, Fabrizio Michelassi, John Hunter, and other members of the board of trustees certainly deserve mention as well. This is not only a group that adds youth to our society leadership, but comes with significant experience in leadership from our sister surgical societies. These are the heroes of the Society for Surgery of the Alimentary Tract who are responsible for maintaining this organization at its high level of achievement and will lead us to a bright future.

MENTORS

There is much overlap between heroes and mentors, but for this purpose, I would like to talk about how GI surgeons, and particularly the SSAT membership, must step to the forefront in the establishment of training opportunities for advanced gastrointestinal and hepatopancreaticobiliary surgery.

First, a little history, and an update on the current status of advanced GI surgical training. The concept of GI fellowships has been spoken of frequently by presidents of our society. Past presidents such as Moody, Cameron, Langer, and Way addressed this issue in their presidential addresses and each advanced the concept closer to reality,[1–4] but it wasn't until Carlos Pellegrini, as president in 2000, took the definitive step in bringing together the three primary GI surgical organizations—the SSAT, the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), and the American Hepato-Pancreato-Biliary Association (AHPBA)—under the leadership of then SSAT education committee chair, Dr. John Hunter.[5] Although it took a couple of years, guidelines for the development of GI fellowships were finally successfully completed. Parallel to this activity, significant progress had also been made, in the area of minimally invasive surgery fellowships, through the Minimally Invasive Surgery Fellowship Council, a spin-off group of SAGES. Fortunately, the Intersociety Tripartite Committee and the MIS Fellowship Council came together with the ultimate creation, two years ago, of the Fellowship Council. Bylaws have been created, the Fellowship Council executive board—made up of representatives of all the societies—has taken a leadership role, and an accreditation committee has been created which has begun, under our new recorder Bruce Schirmer, the process of actual accreditation of existing fellowships. The 2004 match was a tremendous success. Ninety-five programs participated, listing 131 positions. There were 160 applicants for these positions.

Although there have been many fine advanced-GI fellowships available, such as the one mentioned above established by Dr. Langer at Toronto, the program at the Mayo Clinic, and the Hopkins Halsted Chief Year, it was not until 2004 that the first HBP fellowship was available through the new match process. I am very proud that Indiana University was the site of this fellowship. We look very much forward to July when our first fellow will start. It is my understanding that next year many of the existing and more established programs will also participate in the match.

The process has been slow. GI and alimentary tract surgery have always been the bread and butter of general surgery practice. Hesitancy to offend our members in practice or threaten core general surgery training, as defined by the American Board of Surgery, may have lead to delays in the SSAT's implementation of advanced GI fellowships. In our absence, a number of other groups have stepped up to fill the void. Advanced GI surgery fellowships with a focus on the foregut fell under the direction of minimally invasive surgery and led to SAGES and the MIS fellowship council taking the leadership role in establishment of training opportunities. Furthermore, surgical oncology fellowships such as the excellent programs at M.D. Anderson or Memorial Sloan-Kettering clearly are attracting surgical trainees with interest in complex HPB surgery.

Despite the delays in the past, the time is right now for the SSAT and our members to take the lead in the development of advanced GI fellowships. Over the last few years, approximately 70% of graduates of general surgery training programs in the United States have chosen to pursue post-training fellowships. The surgical residents of today are clearly voting with their feet, and the membership of the SSAT must be prepared to offer them the high-quality disease- or organ system-based fellowships. Fellowships should not be procedure- or technique-based, but rather based on an understanding of the pathophysiology of the diseases, the nature of the treatments, whether they are traditional open procedures, minimally invasive, or endoscopic-based therapy, and the assessment and reporting of outcomes. This is the advantage that the membership of the SSAT has in the development of high-quality GI fellowships. To paraphrase from the great baseball movie, *Field of Dreams*, if we build them, they, the surgical trainees, will come.

Further evidence that the time may now be perfect to push forward in establishment of advanced GI fellowships comes from the recommendations proposed by the Blue Ribbon Panel of the American Surgical Association (Fig. 1).[6] In this proposal, after completion of a shortened basic surgery core, trainees will have an opportunity to "track" into specialist training. It would be expected that new advanced training opportunities in HBP, Foregut, and MIS would be necessary to both meet the demand of the trainees and the need for such specialists within the country. Although this training paradigm is a long way from implementation, we must be prepared should the time come.

Finally, advanced GI fellowships have how been legitimized, if not embraced, by the American Board of Surgery. In 2004 at their annual meeting, the American Board of Surgery directors voted to expand the role of the Board in the supervision of advanced surgical training. Although previously the Board had been closely involved with training in vascular surgery, pediatric surgery, and surgical oncology, many areas of advanced training, including minimally invasive, trauma and critical care, and transplantation, have yet to fall under the Board's supervision. Based on this important decision, the ABS, with its strong SSAT representation, has formed a new group of surgical advisory councils. Appointments are currently being made for a Gastrointestinal Surgery Advisory Council, which will consist of two active directors of the American Board of Surgery as well as representatives of five sponsoring organizations—the SSAT, SAGES, AHPBA, The American Society of Bariatric Surgeons, and the Minimally Invasive Surgery Fellowship Council. This group hopes to begin its deliberations in June of this year. I am happy to announce that I have asked Dr. John Hunter, who has a track record of strong leadership in this area, to be our society's representative.

The need for advanced skill levels of GI surgery not only fits with the needs and desires of the surgical trainee, but I believe has become the expectation of the American public and those organizations that pay for medical and surgical care. The concept of centers of excellence or high-volume centers that

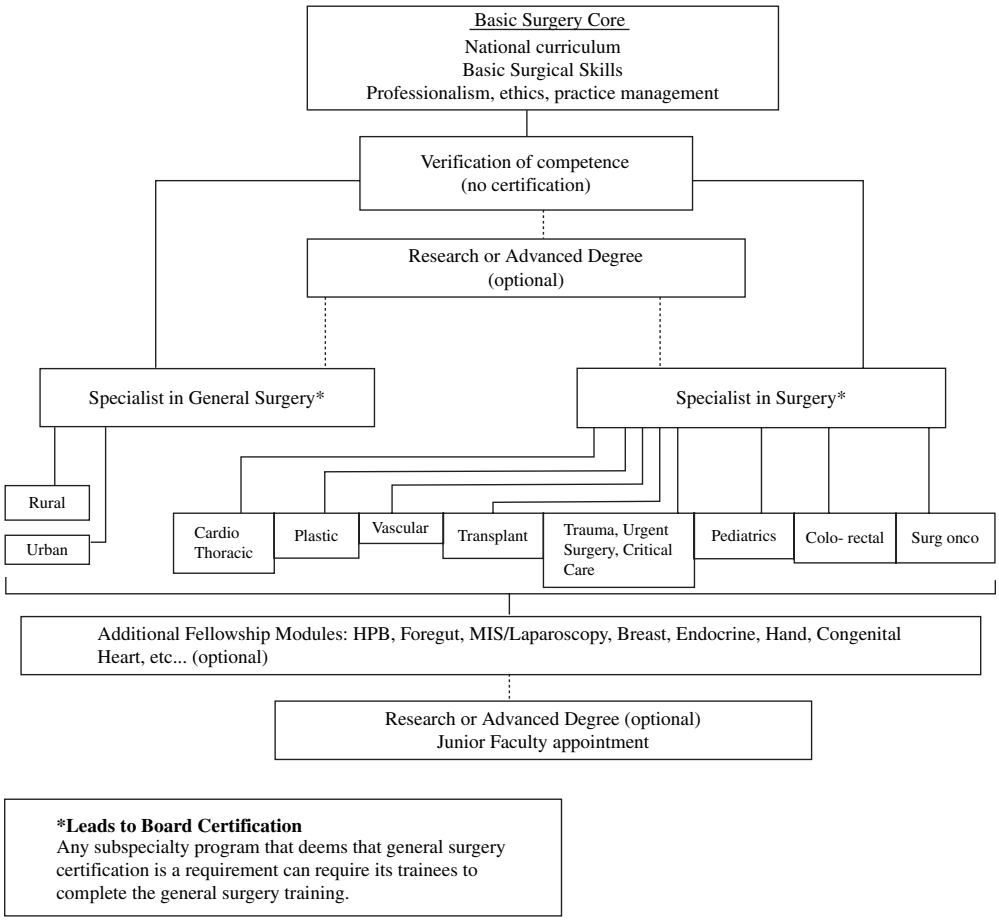

Fig. 1. Proposed schema for restructured surgical residency training.[6]

provide superior results for major GI procedures such as pancreatoduodenectomy, liver resection, and esophageal resection, among other procedures, has been clearly documented in the literature.[7–9] The evidence is so strong that organizations such as Leap Frog have stepped in to try to set levels of volume needed for hospitals to meet their approval. Furthermore, at last month's American Surgical Association meeting, SSAT Board of Trustee member Yuman Fong and his colleagues from Memorial Sloan-Kettering showed that not only are short-term outcomes positively affected by the volume of surgical procedures performed at an institution, but now, at least for pancreatic cancer, there is clear evidence that long-term survival is enhanced in high-volume centers.[10]

Clearly, there is a need for individuals with advanced GI training; but can we deliver these results? What is the track record of advanced GI surgical fellowships? Ask Bernie Langer about the Toronto experience and the success of his graduates; listen to Murray Brennan and Yuman Fong talk proudly of those products from Memorial Sloan-Kettering, finishing with a focus in HPB surgery. Although it may not fit the exact criteria of a fellowship, I can only refer back to what I mentioned before as the Cameron school of GI surgery (Table 1). Fifty-three of the 80 individuals finishing the Johns Hopkins Halsted "Super Chief" year since 1978 continue to practice with a strong clinical focus on advanced GI and HPB surgery. These individuals, many of whom are active members of the SSAT, include two presidents of the society and several who have been, or are, officers, members of the board of trustees, or active members of key committees. Many are recognized as leaders in our field, with many more in the pipeline. I don't think you can find a better example of how an advanced training program can work to produce graduates with a strong clinical focus than the Hopkins program.

Table 1. Cameron "school" of gastrointestinal surgery, 1978–2005

Gregory Bulkley	Warren Maley	Ankesh Nigam
Henry Pitt	Alan Yahanda	Kevin Staveley-O'Carroll
Michael Zinner	Augusto Bastidas	Robert Moesinger
Russell Posteir	Tom Magnuson	Herb Chen
James Sitzmann	Kurt Campbell	Steve Goldin
Michael Sarr	Selwyn Vickers	Max Schmidt
Kenneth Sharp	Steve Ahrendt	Susan DeMeester
Roman Ratych	Jeffrey Drebin	Julie Ann Sosa
Charles Yeo	Paul Lin	Herb Zeh
Keith Lillemoe	Howard Kaufman	Jeffrey Hardacre
David McFadden	Luke Schoeniger	David Efron
Andrew Klein	Kenneth Andreoni	Chandra Are
Mark Talamini	Mark Ott	Eric Nakakura
Jeffrey Peters	Richard Schulick	Martin Mackery
David Crist	Steve Barnes	Gene Kennedy
Pamela Lipsett	Lenny Koniaris	Taylor Sohn-Riall
Eric Wiebke	Attila Nakeeb	Chris Wolfgang
John Meilahn		

My call, therefore, is for the membership of the SSAT to look at your own program, to look at its strengths and its weaknesses, to look at its surgical volumes in key areas, and most importantly to look at the mentors available in complex GI and hepatopancreaticobiliary surgery who exist in your program. If there is the opportunity and the people to lead the way, my hope is to see more and more opportunities developed to train the future leaders of the SSAT and of American GI surgery.

TEAMMATES

Finally, the SSAT must focus on the service provided to the membership of our organization. Over a year and a half ago, the society completed an e-mail–based survey of our membership. Five hundred thirty-eight responses were obtained, representing 34% of the members with known e-mail addresses and 21% of the total membership. Although this may seem like a small percentage, I believe there are some important messages in the data provided.

First, membership in the society is important to those who responded, with over 90% considering membership either very or somewhat important (Fig. 2). The most highly valued component of the SSAT, not surprisingly, is our *Journal of Gastrointestinal Surgery*, which presents not only the papers from this meeting, but outstanding original contributions from our membership as well as other GI surgeons from around the United States and the world (Fig. 3). Interestingly, second most valued is the SSAT program, which seems to be even more valued than the DDW experience in general. But yet, the number of responders who attended our meeting over the last three years is somewhat disappointing, with only 16% of individuals attending the last three consecutive programs and 33% having not attended a single meeting (Fig. 4). Looking at this differently, total membership numbers are shown in Table 2. In general, membership has been steady in the range of about 2,500 members. However, DDW annual attendance of members is less than 20% of the total membership. The factor most important in affecting the decision to attend the SSAT program is topic relevance, followed by location,

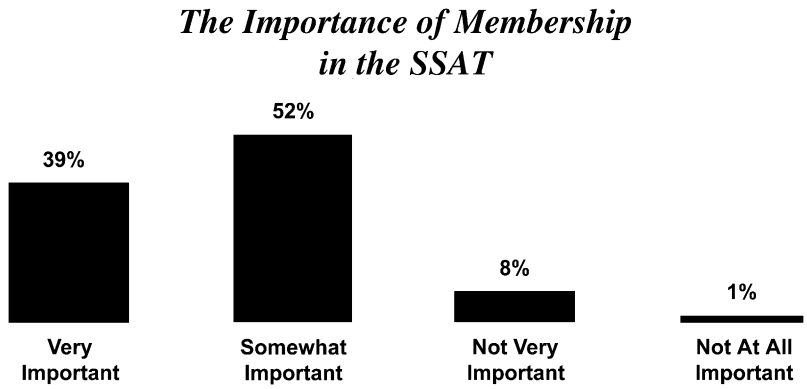

Fig. 2. Importance of SSAT membership based on 2003 membership survey.

conflicts, cost, and quality of the speakers (Fig. 5). It seems obvious, that for whatever reason, our annual meeting does not appear to be very highly valued by over 80% of our membership. This must lead to the question of what, if anything, we can do better to serve them.

Our current annual meeting has been held as part of Digestive Disease Week since 1973. Our teammates at DDW, the American Gastroenterologic Association (AGA), the American Association for the Study of Liver Disease (AASLD), and the American Society for Gastrointestinal Endoscopy (ASGE), have been great partners. DDW is clearly the premier GI meeting in the world, with continuously increasing attendance over the last ten years. Under the strong leadership of SSAT program committee chairs Mike Sarr, Barbara Bass, and David Malvi, we have integrated our program with our other societies. Combined symposiums have become some of the most popular aspects of the meeting, attracting standing-room-only crowds with high-quality discussion from experts representing all disciplines. Without our current teammates, our post-graduate courses would be nowhere near as comprehensive, and attendance would suffer. The combined meeting provides an attractive mechanism for those with a cross-disciplinary interest in basic science research. Nowhere else can such high-quality basic science be presented in a strong clinical venue. Finally, one cannot underestimate the significant financial rewards associated with meetings of this size and with this degree of commercial support.

Clearly, this is a healthy relationship that cannot be disrupted; but we cannot forget that first and foremost we are a group of surgeons, and that a large majority of our membership is not as interested in

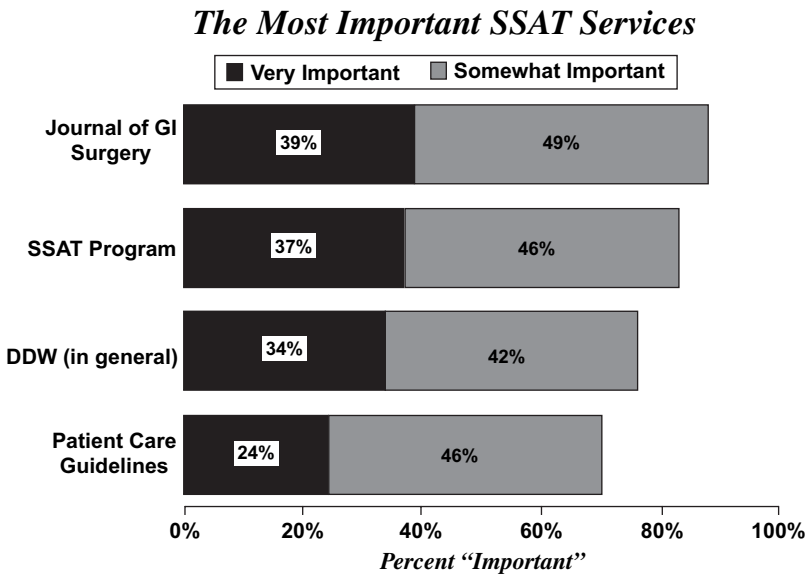

Fig. 3. Important SSAT services based on 2003 membership surgery.

Table 2. SSAT membership And meeting attendance

	Membership	Annual meeting attendance
2002	2529	481
2003	2528	373
2004	2595	394

basic science, or even the multidisciplinary approach to a disease. Their interest lies in the clinical and technical aspects of GI surgery that will directly affect their practice.

Such a philosophy has led to the tremendous growth and vitality of SAGES and their annual meeting. Similarly, anyone who has attended a meeting of the Society of Surgical Oncology has to be impressed with the size of the crowds and the enthusiasm of the participants. In both of these cases, the enthusiasm of these organizations may be enhanced by the feeding of those completing specialty fellowships directly into their membership roles. But if you look at the programs of their meetings, you sense that these groups really try to directly impact their members' practices.

As many of you know, there was an experiment conducted in April 2005 in south Florida. A surgical spring week was held with the combined annual meetings of SAGES and AHPBA with the American College of Surgeons spring meeting. These meetings set all time records for attendance for both organizations. It would appear that the SSAT may have missed a great opportunity to be part of that experiment. Many members of SAGES and most of the members of AHPBA are members of the SSAT. There is also tremendous overlap in the organizations' leadership. Therefore, a year ago I asked then-President Beart to allow the formation of an intersociety task force, including the leadership and representatives of the SSAT, AHPBA, and SAGES. Preliminary discussions have taken place on how these organizations can work together to be teammates in creating a product that better serves all of our membership.

Initial steps have already been taken. At last month's AHPBA meeting, there was a combined SSAT/AHPBA symposium on advanced HPB fellowships. For years, SAGES and the SSAT have worked together for combined symposiums, both at the American College of Surgeons Clinical Congress and at DDW. This year a combined AHPBA/SSAT symposium was held for the first time at DDW, addressing the topic of Advances in Liver Resection for Metastasis.

But where will we go in the future? Can we envision a combined meeting of all three societies? Can we create a surgical Digestive Disease Week? Can we partner, in some form, to enhance each other's meetings and the service that we provide for our membership? One idea that has been proposed is that of regional combined educational programs, scattered throughout the country at different times of the year. The leadership of all three organizations could work together to create an educational product to serve local practitioners without necessitating the cost and time of the travel needed to attend our annual meetings in places like Chicago, San Francisco, and Fort Lauderdale. Can we better use technology to distribute our message by internet and other mechanisms?

These three organizations, and perhaps the colorectal surgeons and the bariatric surgeons, need to consider forming an alliance or become "teammates" to work together to better serve the membership of all of our organizations. Furthermore, active involvement with our sister international societies might also enhance the benefits of membership for GI surgeons around the world. I don't have all the answers, but hope that continued dialog can take place amongst the organizations so that we can be teammates, rather than silos, in advancing the knowledge and developing technology of our specialties.

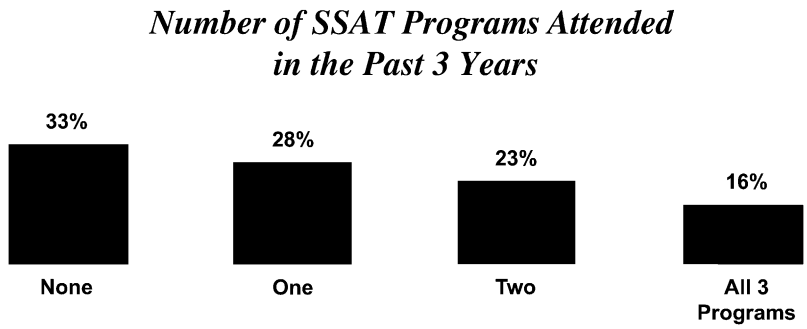

Fig. 4. SSAT meeting attendance based on 2003 membership survey.

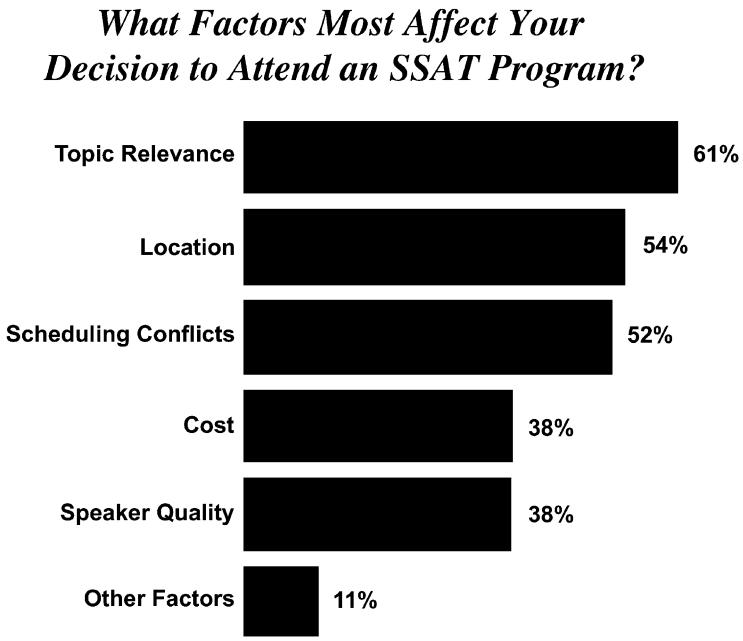

Fig. 5. Factors affecting decision to attend an SSAT program based on 2003 membership survey.

I would encourage all of you, many of who are also members of SAGES, the AHPBA, the Society of Colorectal Surgeons, and American Society of Bariatric Surgery, to give this considerable thought. Please seek the opinion of our membership, especially those who do not come from the traditional academic surgical world and who are probably more disenfranchised by the major meetings than any other group. We have a great relationship with our teammates of DDW, but I think there is room for more. I am anxious to continue to work within the board of trustees and the intersociety working group to come up with new opportunities, and I would very much encourage and solicit your opinions in this matter.

It has been a tremendous honor for me to serve this year as the President of the Society for Surgery of the Alimentary Tract. I appreciate your attention, but more importantly, I hope this address serves as a springboard for those of you who want to be heroes, who want to be mentors, and who want to be teammates in advancing GI surgery for generations to come.

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Robotic-Assisted Heller Myotomy Versus Laparoscopic Heller Myotomy for the Treatment of Esophageal Achalasia: Multicenter Study

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Laparoscopic Heller myotomy (LHM) has become the standard treatment option for achalasia. The incidence of esophageal perforation reported is about 5%–10%. Robotically assisted Heller myotomy (RAHM) is emerging as a safe alternative to LHM. Data comparing the two approaches are scant. The aim of this study was to compare RAHM with LHM in terms of efficacy and safety for treatment of achalasia. A total of 121 patients underwent surgical treatment of achalasia at three institutions. A retrospective review of prospectively collected perioperative data was performed. Patients were divided into two groups: group A (RAHM), 59 patients, and group B (LHM), 62 patients. All the operations were completed using minimally invasive techniques. There were 63 women and 58 men, with a mean age of 45 ± 19 years (14–82 years). Fifty-one percent of patients in group A and 95% of patients in group B reported weight loss. Duration of symptoms was equal for both groups. Dysphagia was the main complaint in both groups (P = NS). There was no difference in preoperative endoscopic treatment in both groups (44% versus 27%, P = NS). Operative time was significantly shorter for LHM in the first half of the experience (141 ± 49 versus 122 ± 44 minutes, $P < .05$). However, in the last 30 cases there was no difference in operative time between the groups (P = NS). Intraoperative complications (esophageal perforation) were more frequent in group B (16% versus 0%). The incidence of postoperative heartburn did not differ by group. There were no deaths. At 18 and 22 months, 92% and 90% of patients had relief of their dysphagia. This study suggests that RAHM is safer than LHM, because it decreases the incidence of esophageal perforation to 0%, even in patients who had previous treatment. At short-term follow-up, relief of dysphagia was equally achieved in both groups. (J GASTROINTEST SURG 2005;9:1020–1030) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Esophageal achalasia, laparoscopic Heller myotomy, robotic-assisted Heller myotomy, complications, swallowing status

Even though achalasia is the most common primary motility disorder of the esophagus, the disease is uncommon, with an estimated annual incidence in the United States of about 1 in 100,000 individuals. The treatment is always palliative and is aimed to decrease the outflow obstruction at the level of the lower esophageal sphincter (LES). Over the years, several treatment alternatives have been proposed, starting with Willis in 1672 who reported the first patient treated with esophageal dilatation,[1] Russel in 1887 described the first balloon dilatation,[1] Heller in 1913 describing the first esophageal myotomy,[1] to Pellegrini and Cuscheri in the early 1990s who described the minimally invasive approach, showing the obvious benefits of reduced morbidity, shorter postoperative hospital stay, and decreased

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postoperative pain.[2,3] Evidence-based medicine has shown surgical treatment as the most effective choice, because the improvement of symptoms following surgery lasts longer.[8–13] Despite encouraging reports supporting the minimally invasive approach, the rate of esophageal perforation has remained nearly as high as those seen with the open techniques (1%–15%) (Table 1).

We first performed robotic assisted surgery in September 2000 and rapidly learned that the presence of three-dimensional image and the suppression of the tremor were important additions to our standard laparoscopic techniques. It was obvious to us that the introduction of robotic technologies for the performance of operations that required a higher degree of skills (e.g., esophageal myotomy) was a logical evolution. Several studies have demonstrated the safety and feasibility of robotics in general surgery. Some of these reports compared conventional laparoscopy with robotic techniques.[4] However, to our knowledge, no report in the literature has compared the application of robotics with the standard laparoscopic techniques for the treatment of esophageal achalasia.

The aim of this study is to compare the efficacy and safety of robotically assisted Heller myotomy (RAHM) with laparoscopic Heller myotomy (LHM) for treatment of achalasia.

MATERIAL AND METHODS

A retrospective review was performed of patients who underwent minimally invasive Heller myotomy for the treatment of esophageal achalasia at the Minimally Invasive Surgery Department of the University of Illinois, Chicago, Hospital de Clinicas Jose de San Martin, Buenos Aires, Argentina, and Hospital Italiano, Mendoza, Argentina. Patients who underwent RAHM constituted group A, and patients who underwent LHM represented group B.

Table 1. Esophageal Mucosa Perforation Rate Among Centers With Large Experience

	No. of Cases	Previous Treatment (n)	Mucosal Perforation (n)	Conversion (n)
Hunter et al., 1997[17]	40	30 (75%)	6 (15%)	0
Patti et al., 1999[10]	133	NA	6 (5%)	1 (1%)
Finley et al., 2001[18]	98	67 (68%)	1 (1%)	0
Zaninotto et al., 2001[19]	100	10 (10%)	5 (5%)	6 (6%)
Bloomston et al., 2001[20]	111	88 (79%)	8 (7%)	3 (3%)
Sharp et al., 2002[21]	100	74 (74%)	8 (8%)	3 (3%)
Total	542		28 (5%)	13 (2%)

Preoperative Evaluation

The diagnosis of achalasia was made based on symptoms, barium swallow, and upper endoscopy. However; the definitive diagnosis was always made by means of esophageal manometry.

Symptomatic Assessment

Cardinal symptoms were dysphagia, regurgitation, chest pain, and heartburn. Before and after surgery, patients scored their symptoms using a five-point symptom score according to frequency, ranging from 0 (never) to 1 (once a month), 2 (once a week), 3 (once a day), and 4 (several times a day). The swallowing status was graded as follows: excellent (no dysphagia), good (occasional dysphagia), fair (frequent dysphagia), and poor (severe dysphagia).

Barium Esophagogram

A barium swallow was routinely done during the initial examination and was often accompanied by fluoroscopic assessment. The study demonstrated the typical features of achalasia (i.e., tapering at the level of the gastroesophageal junction or "bird's beak" and esophageal dilation) in 85% of patients. Sigmoid esophagus was present in 7% of patients. One patient had an epiphrenic diverticula and one patient presented with hiatal hernia in addition to achalasia.

Upper Endoscopy

Exclusion of mechanical obstruction or mucosal damage was performed by endoscopy. The importance of detecting tumors causing pseudoachalasia has already been described.[5]

Esophageal Manometry

A four-channel water-perfused motility catheter with 5-cm spacing between sensors was passed via either the nares or the mouth into the stomach, following which a station pull-through technique was used to assess the LES and the esophageal body. The esophageal body was assessed with 10 consecutive wet swallows. LES pressure (normal = 14–24 mm Hg), LES relaxation, and esophageal body

proximal and distal amplitude and duration were assessed.

Surgical Technique

Robotic-Assisted Heller Myotomy

The operative technique for RAHM has been previously described.[6] After satisfactory induction of general endotracheal anesthesia, the patient is placed in the semilithotomy position over a "bean bag." The room set-up is shown in Figure 1. Trocar placement is similar to that for LHM and is identical for every advanced esophageal procedure, with a camera port placed 2 cm to the left of the umbilicus, approximately two finger-breadths above the umbilicus.

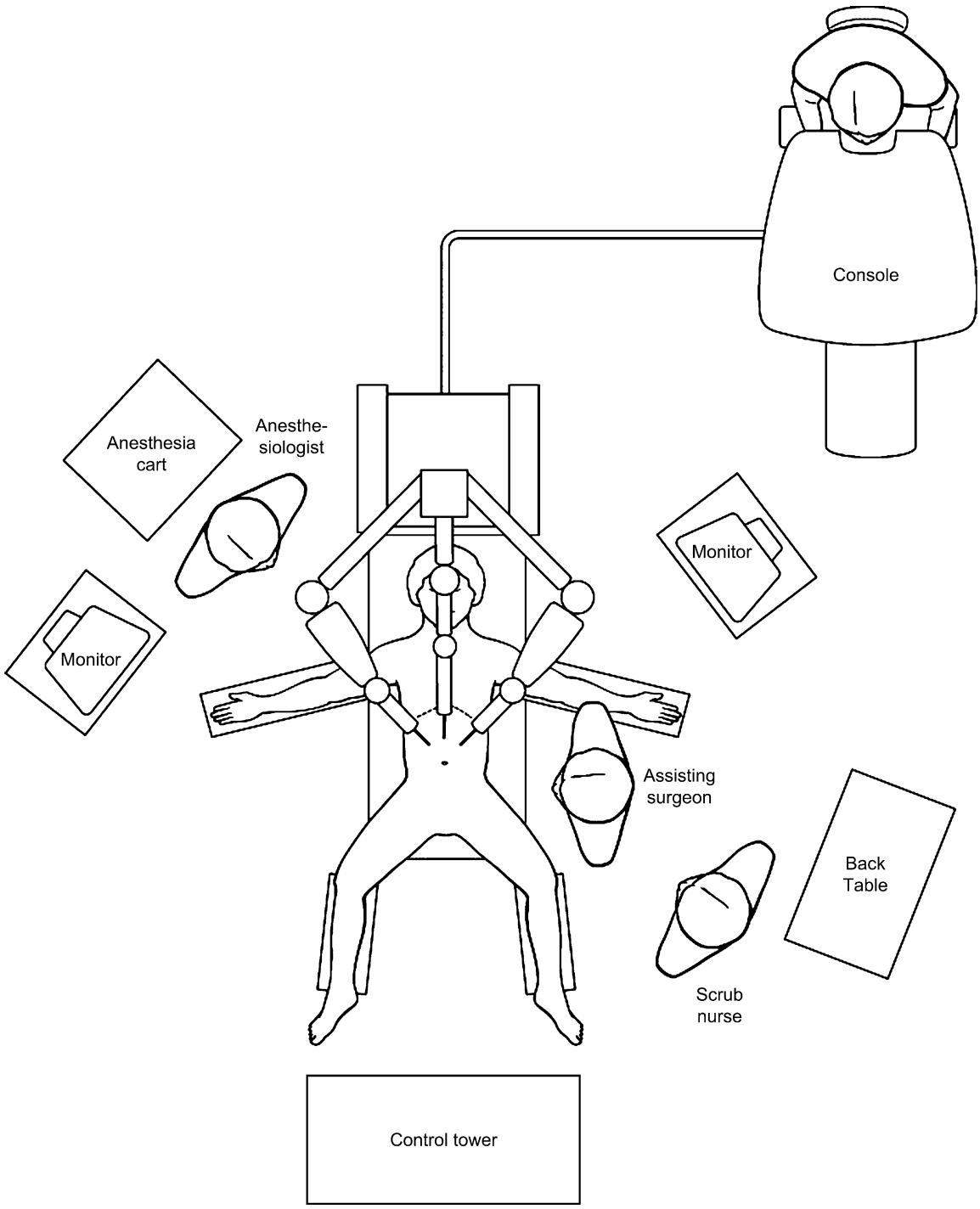

Fig. 1. Operating room set-up.

Two 8-mm trocars are placed in the right and left upper quadrant in the midclavicular line for the two robotic arms. A 0.5-cm incision is made in the subxyphoid area, and the left lobe of the liver is then retracted anteriorly using the Nathanson liver retractor. An assistant port is placed in the left anterior axillary line 2 cm below the costal margin. Pneumoperitoneum is induced through an incision using the camera port. At this point, the nursing personnel approximate the robotic surgical cart into position and the arms of the robot are attached to the three specific trocars. The set-up of the robot is usually performed by the assistant at the bedside. The left crura approach is routinely used. The operation is started by dissecting the left and right crura and dividing the proximal short gastric vessels using the harmonic scalpel. Only the anterior part of the esophagus is dissected, respecting the posterior attachments. After passing a 44 Fr bougie through the mouth, the fat pad is removed to better expose the gastroesophageal junction. The anterior branch of the vagus nerve is mobilized from the esophageal wall. The myotomy is started out just above the gastroesophageal junction on the 12 o'clock position using the robotic articulated hook electrocautery (Fig. 2). The submucosal plane is reached in one point. This is followed by extending the myotomy a minimum of 6 cm proximally and for about 2–3 cm distally into the stomach (Fig. 3). The preferred antireflux operation is the Dor fundoplication, which is an anterior 180° fundoplication.[7] The Dor fundoplication is composed of two rows of sutures. The first stitch on the left side includes the gastric fundus, the left crura, and the left side of the myotomy. The remaining two stitches include the stomach and the left edge of the myotomy. The second row of sutures is created in the same fashion; by placing the first stitch incorporates the gastric fundus, the right crura, and the right side of the myotomy. Two stitches are then placed between the stomach and the right edge of the myotomy.

Laparoscopic Heller Myotomy

After satisfactory induction of general endotracheal anesthesia, the patient is placed in low lithotomy position with the legs on stirrups. Trocar placement is similar to that for RAHM. Pneumoperitoneum is induced with CO_2 through the camera

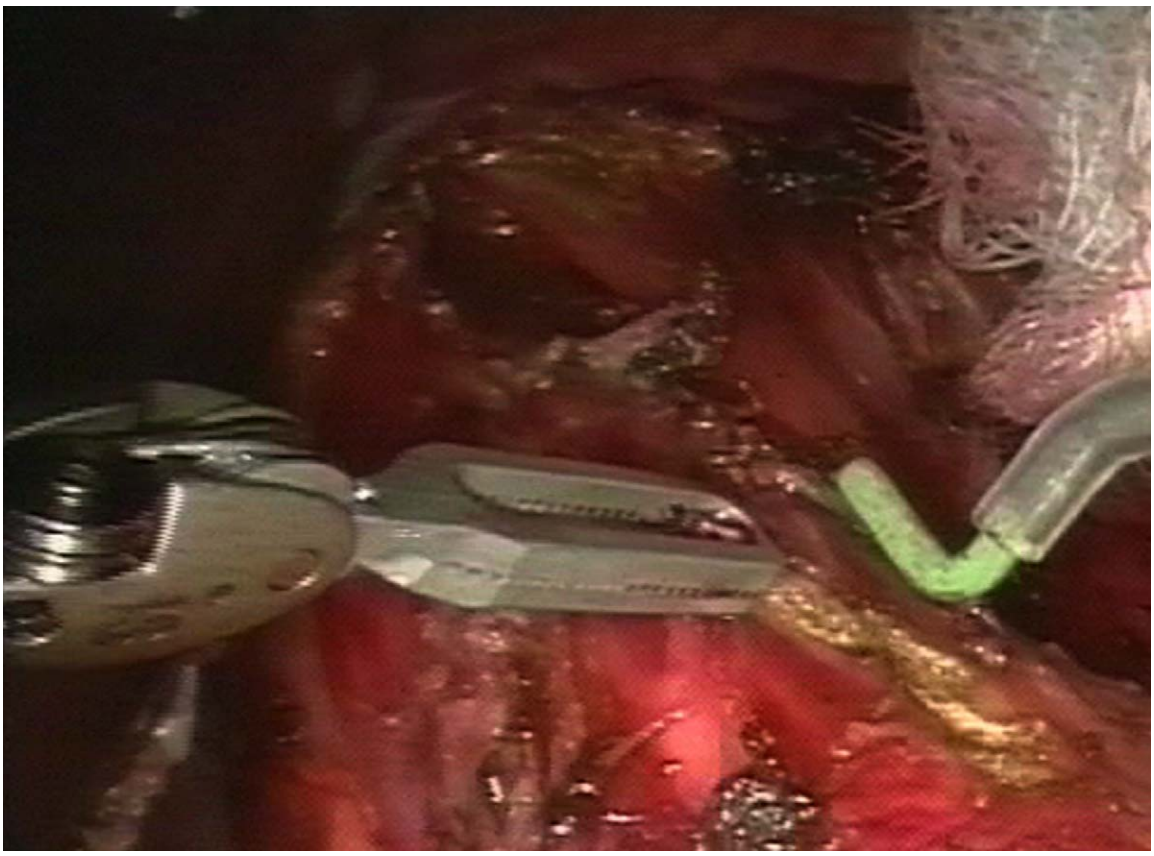

Fig. 2. Beginning of the esophageal myotomy at the gastroesophageal junction, using the Da Vinci specific instruments.

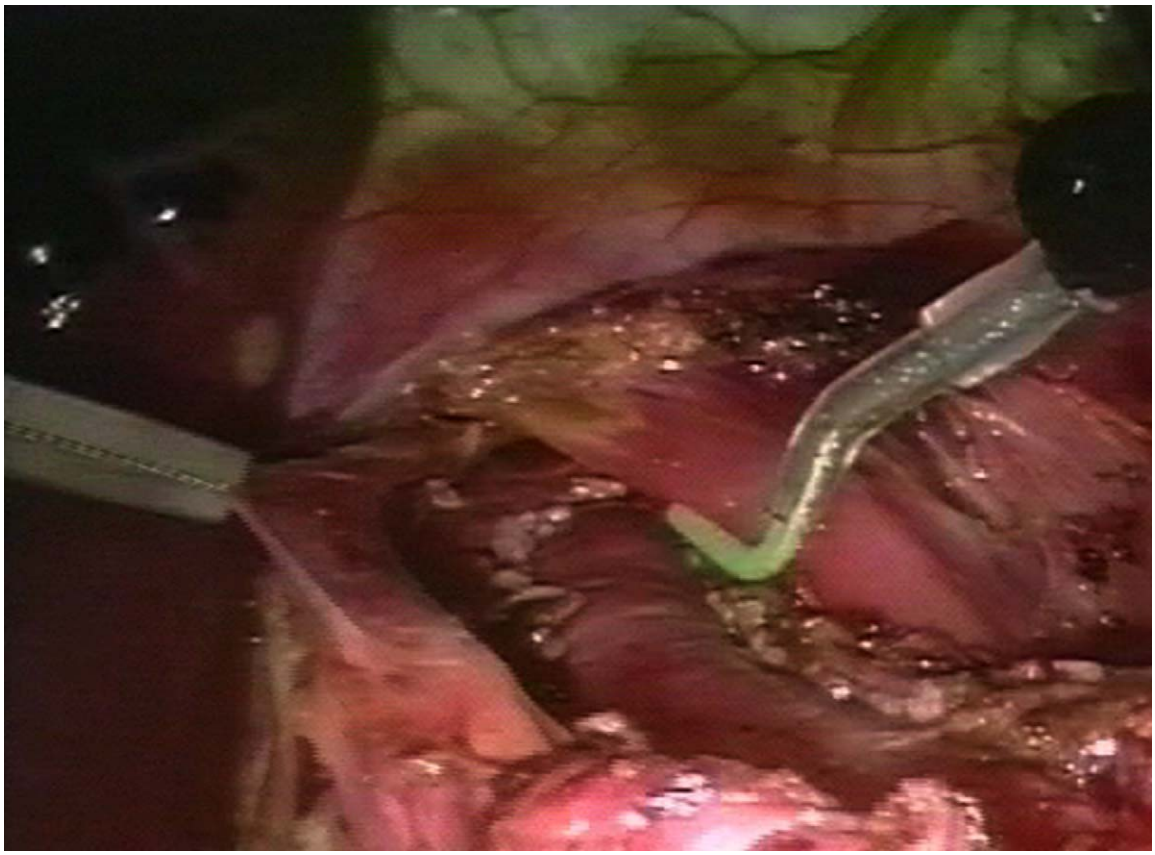

Fig. 3. Finalized robotically assisted Heller myotomy, extending a minimum of 6 cm proximally and for about 2 cm distally into the stomach.

port. The operation is started by dissecting the left crura from the esophagus. After this, the top short gastric vessels are taken down using the harmonic scalpel. Anterior and lateral dissection of the esophagus is routinely carried out, extending well into the thorax in order to complete the myotomy; no posterior dissection of the esophagus is performed. Once a 44 Fr bougie is inserted into the esophagus, the operation is similar to the one described earlier. The hook electrocautery is used to perform the myotomy and the Endostitch (US Surgical Corp., Norwalk, CT) to perform the fundoplication. Perforations were closed using 4-0 silk using laparoscopic suturing techniques when appropriate.

Follow-up

Patients were seen in follow-up 1 week after surgery and every 3 months for the first year. After this, patients were seen at regular 6-month intervals or they were contacted by telephone interview. Detailed symptomatic evaluation was obtained during each follow-up visit. Follow-up was available in 89% of patients after LHM and in 90% of patients after RAHM. Of the entire group, 70% of patients had 12 months or more of follow-up. The total length of follow-up was 22 ± 16 months for the laparoscopic group and 18 ± 11 months for patients who underwent RAHM.

Statistical Analysis

The groups were compared using χ^2, Student's t test, and analysis of variance as indicated. Paired Student's t test was used for observation before and after treatment in the same individual. All results are expressed as mean ± standard deviation unless otherwise stated. Differences were considered significant at $P < .05$.

RESULTS

Laparoscopic Heller Myotomy

Between August 1995 and November 2004, 62 patients underwent LHM at the Department of General Surgery of the Hospital de Clínicas Jose de San Martin, Buenos Aires, Argentina, and Hospital Italiano, Mendoza, Argentina. Thirty-three

(53%) patients were female and 29 (47%) patients were male. Average age was 48 ± 19 (range, 15–82 years). These patients were symptomatic for an average of 56 ± 67 months. Weight loss was reported in 95% of patients. Additionally, in this group 10 patients had Chagas disease (Table 2).

Seventeen patients (27%) underwent previous endoscopic intervention. Sixteen of them (94%) underwent pneumatic dilatation and only 1 patient had botulinum toxin type A (Botox) (6%).

Operative and Postoperative Course

The operation was completed laparoscopically in 61 (98%) patients. Operative time was 122 ± 44 minutes, decreasing to an average of 104 minutes in the last 30 cases. The most common intraoperative complication was esophageal mucosa perforation. This complication was observed in 10 (16%) patients and it was repaired laparoscopically in 9 patients. In one patient the repair could not be accomplished laparoscopically and conversion to an open procedure was necessary. One patient developed intraoperative bleeding during the takedown of the short gastric vessels. No conversion was needed in this case. On postoperative day 2, one patient developed postoperative pneumonia, which resolved with a 7-day course of antibiotics. Blood loss averaged 32 ml (10–100 ml). Patients were given clear liquids the morning following surgery. Mean length of hospital stay was 2.2 days (1.0–8.0 days), with 79% of patients discharged within 48 hours. No deaths related to the procedure were observed. One patient died from laryngeal carcinoma 1 year after surgery.

Table 2. Comparison Between Group A (Probotic = Assisted Heller Myotomy) and Group B (Laparoscopic Heller Myotomy)

	Group A (n = 59)	Group B (n = 62)	*P* Value
Age	42 ± 19	48 ± 19	.09
Duration of symptoms	64 ± 78	56 ± 67	.55
Weight loss (% of patients)	51	95	<.01*
Dysphagia (% of patients)	100	100	1
Previous treatment (% of patients)	44	27	.08
LESP (mm Hg)			
Preoperative	33 ± 13	26 ± 6	<.01*
Postoperative	7.1 ± 3.8	10 ± 1.5	<.01*
Operative time (min)	141 ± 49†	122 ± 44†	.03*
Esophageal perforation (% of patients)	0	16	<.01*
Postop GERD (% of patients)	17	16	.9
Good/excellent (% of patients)	92	90	.5

LESP = lower esophageal sphincter pressure; GERD = gastroesophageal reflux disease.
*$P \leqslant .05$.
†Last 30 cases group A versus group B ($P = .5$).

Symptomatic Assessment

All the patients experienced dysphagia as their most frequent symptom, and 79% of patients experienced regurgitation in addition to dysphagia. They were symptomatic for an average of 56 ± 67 months. The severity score for dysphagia was 2.9 ± 0.7. Patients who received endoscopic treatment before surgery were older, and experienced symptoms for longer periods of time compared with patients who did not received prior interventions. After surgery, 48 patients (90%) considered their swallowing status as good or excellent at the mean follow-up of 22 months. The severity of dysphagia decreased to 0.3 ± 0.7 ($P < .001$). No patient required additional endoscopic or surgical treatment in this group. However, two patients required upper endoscopy for food impaction. Ten patients (16%) experienced symptoms of gastroesophageal reflux. These patients were appropriately managed with proton pump inhibitors.

Manometric Evaluation

All the patients underwent esophageal manometry in the preoperative evaluation. The LES resting pressure was hypertensive in 48% of patients and normal in 52% of patients. Overall, the LES pressure was 26 ± 6 mm Hg. The LES relaxation was either absent or incomplete in every patient. After the esophageal myotomy, the LES pressure decreased substantially (10 ± 1.5, $P = .01$), regardless of whether patients underwent previous treatment or not. Esophageal body peristalsis was absent in all cases before and after surgery.

Robotically Assisted Heller Myotomy

A total of 59 consecutive patients underwent RAHM for the treatment of esophageal achalasia at the Minimally Invasive Surgery Center at the University of Illinois. Thirty patients (51%) were female and 29 (49%) were male. Mean age was 42 ± 19 years (range, 14–82 years). Weight loss was reported by 51% of patients in this group.

Twenty-six patients (44%) had previous endoscopic treatment before surgery before RAHM (group A). Seventeen patients (65%) had pneumatic dilation, four patients (15%) had Botox injection, and five patients (20%) had both procedures. In addition, in this group, one patient had a previous open transthoracic Heller myotomy 17 years prior to the referral. One additional patient had LHM with

Toupet fundoplication 2 years prior to the robotically assisted operation.

Operative and Postoperative Course

The operation was completed laparoscopically with the assistance of the robotic system in all the patients. Operative time was 141 ± 49 minutes, including robotic set-up time (i.e., draping of the arms of the robot, surgical cart positioning, and instruments set-up). In the last 30 cases, the overall operative time decreased to 108 minutes. No mucosal perforations were observed. Two patients (3.7%) developed postoperative complications. One patient developed an incarcerated incisional hernia through the port site on postoperative day 4. A second patient had a delayed perforation of the transverse colon requiring partial colectomy. Upon review of the operation, we did note that the patient had right upper quadrant adhesions, which were taken down under direct vision using the harmonic scalpel, and we hypothesized that a thermal injury to the bowel could be the cause of this clinical picture. It is worth highlighting that the duration of the operation in patients who received prior endoscopic intervention was an average of 45 minutes longer. Blood loss averaged 22 ml (5–80 ml). There were no conversions to open procedures or to conventional laparoscopy. Patients were given clear liquids the night of the operation. Mean length of hospital stay was 1.5 days (range, 0.8–4 days), with 85% of patients discharged within 48 hours. There were no deaths in this cohort.

Symptomatic Assessment

All of the patients experienced dysphagia as their most frequent symptom, regurgitation being the second most frequent symptom (78%). Patients experienced symptoms for an average of 64 months (range, 3–300 months). Patients who had prior unsuccessful endoscopic treatment were older and had had their symptoms considerable longer when compared with their untreated counterparts. After surgery, 50 patients (92%) considered their swallowing status as good or excellent at the mean follow-up of 18 months. The severity of dysphagia decreased significantly from 3.6 ± 0.6 preoperatively to 0.4 ± 0.8 postoperatively.

Additional endoscopic treatment was necessary in two patients; one of them had recurrent dysphagia 8 months after surgery, and the other had persistent dysphagia 2 months after surgery. Pneumatic dilatation was performed, and both patients obtained complete relief of symptoms.

Ten patients (17%) complained of gastroesophageal reflux symptoms after surgery. All of these patients were offered the opportunity to undertake a pH monitoring study. Of the five patients who consented to undergo the study, only one (20%) had an abnormal DeMeester score. These patients were treated with proton pump inhibitors with good outcomes.

Manometric Evaluation

Esophageal manometry data were available in 56 (95%) patients before surgery. The LES resting pressure was hypertensive in 67% of patients and normal in 32% of patients. Only one patient had LES pressure less than 10 mm Hg in this cohort. This patient had both pneumatic dilatation and Botox injections preoperatively. Overall, the LES pressure was 33 ± 13 mm Hg. The LES relaxation was absent in 47% of patients and partial in 53% of patients. After surgery, the LES pressure decreased considerably (7.1 ± 3.8, $P = .01$), regardless of whether patients underwent previous treatment. Esophageal body peristalsis was absent in all of the patients before and after surgery.

DISCUSSION

The aim of therapy for achalasia is to relieve the resistance at the level of the LES and to improve esophageal emptying. During the 1970s and 1980s, the first option for treatment was pneumatic dilatation. The alternative approach and the procedure of choice for those with advanced disease or patients who failed dilatations was Heller myotomy. In the early 1980s, Csendes and colleagues demonstrated that performing a transabdominal anterior esophageal myotomy prevailed over balloon dilatation, offering adequate long-lasting results in 90%–95% of patients.[8,9] However, surgery was not without disadvantages, and these included morbidity, mortality, the need for general anesthesia, and a long hospitalization period. All of these drawbacks were defeated by the introduction of minimally invasive surgery in the field.[2,3] The laparoscopic approach offered results at least as good as those from open procedures, yielding, in addition, less postoperative pain, shorter hospital stay, shorter disability, lower cost, and a better cosmetic result than the open approach.[10] Furthermore, the application of these techniques have almost permanently shifted the treatment algorithm of the disease,[11] making LHM the operation of choice. In the current study, good or excellent results were obtained in 90% of patients of group A and 92% of patients of group B. In order to obtain optimal results, however, important technical principles should be observed while performing the operation, such as complete mobilization of the fundus of the

stomach by dividing the short gastric vessels, adequate extension of the myotomy (i.e., 6 cm into the distal esophagus and 2–3 cm into the gastric wall), and the addition of a fundoplication (Dor or Toupet). Some of these essential technical aspects are still a matter of debate. For instance, Oelschlager and colleagues[12] underlined the importance of prolonging the myotomy 2 to 3 cm below the gastroesophageal junction in preventing postoperative dysphagia. Yet the extension of the myotomy onto the proximal stomach continues to be the most difficult and important part of the operation. The changing in direction of the muscular fibers, from circular of the esophagus to oblique at the stomach, makes it difficult to develop the necessary submucosal plane to divide the muscular fibers and bleeding is more likely. These difficulties may elucidate why, in most series, esophageal mucosa perforation takes place at the gastroesophageal junction or below, and not in the mediastinum (Fig. 4). The laparoscopic approach provides a magnified operative field, increasing the accuracy and improving the exposure during this maneuver. Perforation rates are variable, ranging from 1% to 15% in centers with large experience, being the most common intraoperative complication reported (Table 1). Several authors consider that preoperative endoscopic treatment adversely affects the results of LHM and draw a parallel between the occurrence of mucosal perforations and prior esophageal instrumentations.[13,14] In the present study, mucosal perforation occurred in 10 (16%) patients in the laparoscopic group. In this group, only 30% of patients in the laparoscopic group who had mucosal tear underwent previous endoscopic treatment, and for the most part, esophageal perforations occurred during the first part of the experience. This suggests that factors other than mere previous endoscopic treatment or the effect of the learning curve could play a role in the frequency of this cumbersome complication. Perhaps the natural impediments of laparoscopic surgery and the physical challenges that surgeons endure with minimally invasive techniques can elucidate this dilemma. In the robotic-assisted group, no esophageal perforation was observed either linked to the number of cases performed or related to previous endoscopic treatment, and operative times were similar to those of LHM after the first 30 cases. Several factors may

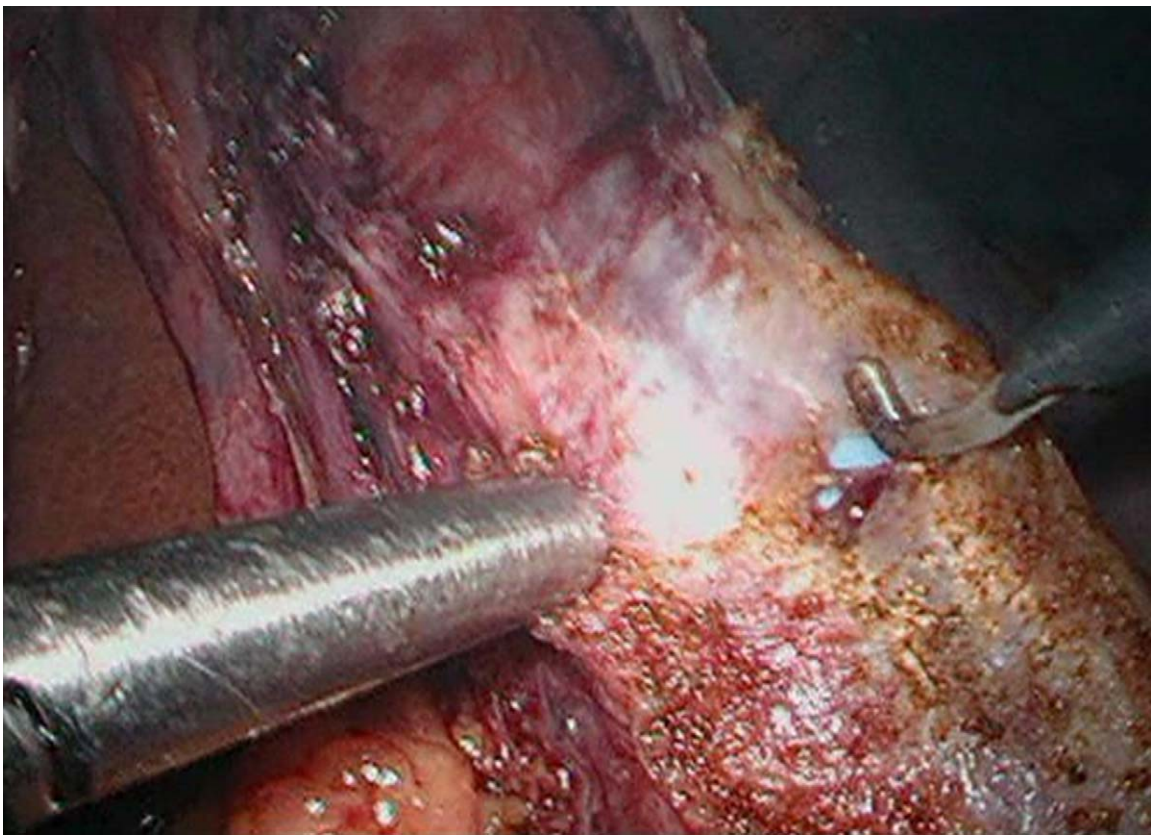

Fig. 4. Esophageal mucosa perforation during laparoscopic Heller myotomy.

have played a role in decreasing the morbidity of the procedure. First, elimination of the tremor of the human wrist, freedom of movement of the articulated instruments, and three-dimensional vision allowed us to visualize and divide each individual muscular fiber, ensuring an adequate and safe myotomy. Second, another important advantage is restoration of proper hand-eye coordination. Finally, in order to decrease the incidence of perforation, we perform the myotomy by spreading and tearing the circular fibers, avoiding the use of the hook cautery as much as possible, and subsequently reducing the risk of intraoperative or delayed perforation. We have no doubt that the three-dimensional image plays a very important role in avoiding perforations in patients with previous endoscopic treatment. This experience is supported by our multicenter study of robotic myotomies for the treatment of achalasia, involving the University of Illinois, Ohio State University, and Johns Hopkins University, where in 104 robotic myotomies, no perforations were found.[15]

The other important point to consider is that the majority of the conversions to open surgery reported during LHM are required due to the intraoperative recognition of a mucosal tear in addition to the complexity of laparoscopic repair (Table 1). The emergence of robotics has the potential to eradicate those impediments, allowing the repair to be performed in a better fashion with a better result. Chang et al.[16] demonstrated that with the assistance of the robotic system, surgeons can exceed their laparoscopic performance, completing intracorporeal knots better and faster. These attributes of the robotic system have been of great significance in our practice by decreasing morbidity without sacrificing efficacy at least at short-term follow-up.

There are still several disadvantages to these systems. The setup, which includes the sterile draping, the cart positioning, and the attachment of the trocar, is time consuming. In this cohort, this was reduced with the experience of the operating room team after the first 30 cases. Other limitations are the lack of tactile feedback and transiently the lack of compatible instruments.

Certain limitations of our study must be acknowledged. First, this is a nonrandomized comparison study. Second, it can be argued that our analysis of outcomes is limited by small number of patients. On the other hand, the fact that esophageal achalasia is a very uncommon disease and that there is alternative nonsurgical treatment precludes general surgeons from extensive exposure to many of these procedures. As a result, only a few centers worldwide have a large experience in the management of achalasia of the esophagus.

CONCLUSION

RAHM provides similar outcomes in terms of symptoms relief compared with LHM. When the rate of intraoperative complications was compared in this prospective nonrandomized study, the use of computer-enhanced technology appears to have decreased the rate of esophageal mucosa perforation. Randomized control trials comparing these therapeutic alternatives are needed to support these preliminary findings.

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Discussion

Dr. Carlos Pellegrini (Seattle, WA): I would like to frame my discussion into two separate parts: one is the analysis of the paper and the data, the conclusions, and the results, and the other one is what I believe is my personal view on the use of the robotic-assisted laparoscopic approach to achalasia patients.

So for the first part, what you have seen is that the authors have shown you two groups of patients, approximately 60 patients in each of the arms. Since the duration of symptoms and the disease, the preoperative treatments, and so forth appear to be the same in the two groups of patients, the populations are assumed to be similar. In reality, however, these patients were operated on at two different institutions, at two different times, and by surgeons with different experience. Thus, the striking difference in the perforation rate, 0% versus 16%, is not as easy to interpret. I believe that the most important element that determines the perforation rate is the surgeon's experience.

It seems to me, given that you are comparing the initial experience in two centers in Latin America with the experience here in Illinois, knowing that you have significant experience with achalasia treatment, that the experience of the surgeon might be a factor involved here to a greater extent than the use of the robotic-assisted technology. In fact, if you look at the table that you presented today, a perforation rate of 16% is the highest rate of any of the large series. We have 5%. Most people today accept 5% or less as a perforation rate, and I would submit to you that with more experience that can be decreased to that level at least.

So I would ask you to comment on the role that you think the experience, you versus the others who personally did this, had to do with this issue?

The second part of my discussion addresses what I believe is the application of robotic technology, and one could assume from what I just said that I am against it. Well, I am not. In fact, I believe that the authors are correct in that the three—dimensional view that one gets with the robot, and in particular, in achalasia patients where the details of the operation are so important, the ability to operate with an absolute complete view of the arm and the ability of the arm to rotate the way it does—it seems to me intuitively that it gives us an advantage. I have used the robot in achalasia patients and have found it to be useful.

Achalasia surgery is the place where I can see the potential for the greatest benefit in the application of robotics. In addition, I think that the robot or the robotic technology is, as Richard Satava has referred to, an information system with arms, just like the CT scan is an information system with eyes, and therefore the potential in the future for the use of robotic technology is extraordinary.

However, I am concerned with the current status of the robot, and I wonder if you would comment on three issues.

One is the fact that as it is currently configured, you need an assistant to do this operation from the table side, and the assistant has to be a fairly experienced person. I have found that if you have someone who is not experienced, the ability of the person in the console is significantly compromised. The assistant, furthermore, is in a position of interacting directly with robots. That is contrary to any other robotic technology that is around. In industry when a robot is devised, the robot works with itself; nobody puts their hands in there. When I am helping my assistant with a robot, I end up with my hands being banged constantly by the right and the left arm of the robot. So is there something in the pipeline that would eliminate the need for the assistant?

The second issue has to do with instrument change. In its current format it is rather complex and I find that I frequently keep using the same instrument over and over just because I don't want the time or the risk involved in changing the instrument. Indeed, we have had injuries to the liver and one duodenal perforation that are attributed to the instrument change. With that in mind I was

wondering if the colonic perforation you had was not also related to instrument change?

The entrance of the instrument with this instrumentation today is a bit dangerous and I am wondering if we have something that might facilitate that.

The third issue is how do you teach this in a safe manner? We need to have a separate second console for the learner, as I think that is so important.

I do want to recognize that Dr. Horgan was actually the pioneer who started the routine application of these procedures to the esophagus and, along with Mark Talamini, of course, have shown us all the way. Thank you very much.

Dr. Horgan: Thank you very much for the comments, and I was expecting those tough questions having had you as a mentor for many years.

With regard to your first comment regarding experience, we did think about that. We have the fellows performing the myotomy in the robotic group, and we know that they have almost no experience when they do the myotomy and they still don't perforate the esophagus. So having said that, we do believe that even with the unexperienced surgeon, robotic myotomy does make a difference. If, on the other hand, when asked, Phil Donahue in our group, who has a lot of experience with laparoscopic surgery, agrees also with Marco Patti that the perforation rate in their hands was not related to experience.

We did find out that when we compared advanced skills in the lab that surgical residents do much better suturing with the robot than they did with the laparoscope. That is something that your group has also found in Seattle. So we may think that experience plays a role, but we don't see that.

With regard to the assistant and the robot, we do agree that at the beginning of the learning curve with robotic surgery, one feels much more unsafe or insecure with who is assisting, and we want to have as good an assistant as you have a surgeon. But the new system has four arms, and four arms allows you to do solo surgery, and that we have proved and we have shown at the American College of Surgeons meeting with esophageal leiomyoma or even Nissen fundoplication where the assistant was of a low resident entry level.

One needs to control how your instruments are coming in and out because you don't have a good view, even though the new technology allows you to switch from the control central image to a panoramic image by the flip of a pedal. This is a new software update.

Regarding instrumentation, this has been a problem with robotics. We started doing this operation in 2000; we have done more than 500 cases right now, and we have been working with a company in trying to develop suction irrigation devices and endostapler devices that will allow us to really do purely solo surgery, and in the evolution we will have a suction irrigation device very soon and address this problem.

Our colonic perforation was a delayed ischemic perforation with a Harmonic scalpel. It was not due to banging into the colon with an instrument.

We do agree with you on how you teach this technology. We felt that teaching laparoscopy was stressful; well, when you teach robotics, they have full control of your Ferrari and they can go 400 miles an hour if they want to. A second console is important here. Based on what we have learned with airplanes, we are in an evolution of technology. Having said this, we do have a second system in the lab, where we train our fellows and residents so when they come to the operating room they already know what to do.

Esophagogastrectomy: The Influence of Stapled Versus Hand-Sewn Anastomosis on Outcome

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Successful anastomosis is essential for favorable esophagogastrectomy outcomes. Before July 2002, almost all esophagogastric anastomoses at our institution were hand-sewn. We then began using linear stapled anastomotic techniques. This review compares patient outcomes with both techniques. From July 2001 to June 2004, 280 consecutive esophagogastrectomy patients (235 men and 45 women) were reviewed (median age, 65 years). The anastomosis was intrathoracic in 206 patients (74%) and cervical in 74 (26%). Anastomoses were hand-sewn in 205 patients (73%) and linear stapled in 75 (27%). Stapled anastomoses were intrathoracic in 33 patients (16%) and cervical in 42 (57%). Anastomotic leaks occurred in 30 patients (11%); 26 (12.7%) in the hand-sewn and 4 (5.3%) in the linear stapled group ($P = .008$). Leaks were asymptomatic in 17 patients (57%). Dilatation was required in 70 hand-sewn anastomoses (34%) and in 11 stapled (14.6%) ($P = .001$). Hand-sewn anastomoses were more likely to leak and require dilatation; odds ratios and 95% confidence intervals were 5.35 (1.67–19.27) and 3.58 (1.66–8.34), respectively. A linear stapled anastomosis is safe and associated with both a significantly lower leak rate and the need for dilatation compared with hand-sewn anastomosis. This nonrandomized series suggests that linear stapled anastomosis is the preferred technique regardless of anastomotic location. (J GASTROINTEST SURG 2005;9:1031–1042) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Anastomosis, esophageal cancer, esophagectomy, Ivor Lewis, transhiatal, stapler

Opinions vary regarding the optimal location and technical aspects of hand-sewn anastomoses (HSA) versus linear stapled anastomoses (LSA) following esophagogastrectomy.[1–7] Regardless of the surgical approach, avoiding anastomotic complications is essential for minimizing early morbidity and maximizing long-term functional results and quality of life.[8,9] Short-term devastating complications include ischemia and leak, while long-term complications include stricture formation.[10] Anastomotic leak following esophagogastrectomy has been reported to occur in 5%–15% of patients and anastomotic stricture in 30%–50% of patients.[11–13] Both of these complications negatively impact quality of life [8,9,13,14]

In 1988, W. Spencer Payne, M.D., at the Mayo Clinic proposed using a linear stapler for creation of the posterior portion of the cervical anastomosis in transhiatal esophagogastrectomy (Fig. 1). He believed that the wide posterior triangulated opening created with the linear stapler made stricture formation less likely. At that time, manipulation of the available linear staplers in the neck proved to be awkward. As a result, the majority of esophagogastric anastomoses at our institution continued to be HSA. With the advent of smaller endoscopic staplers, manipulation in the chest and neck became simpler, and in 2002 we began using LSA for esophagogastric anastomoses. The purpose of this review is to compare our outcomes for patients with HSA and LSA following esophagogastrectomy.

MATERIAL AND METHODS

Between July 1, 2001, and June 30, 2004, 280 patients underwent esophagogastrectomy with gastric conduit reconstruction at the Mayo Clinic in Rochester, Minnesota. Patients who had esophagogastrectomy and reconstruction with colonic or small bowel transposition and patients who had

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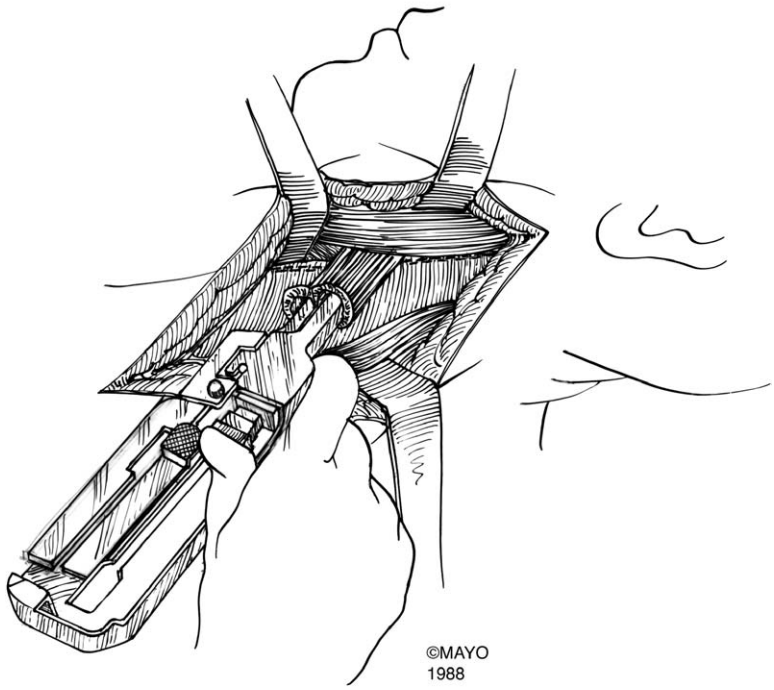

Fig. 1. W. Spencer Payne's 1988 illustration of stapled cervical esophagogastric anastomosis.

reestablishment of gastrointestinal continuity following failed esophagogastrectomy were excluded. The medical records of these patients were reviewed for age, gender, indication for esophagogastrectomy, neoadjuvant therapy, operative procedure, type of anastomotic reconstruction, surgeon, pathologic diagnosis, TNM stage, perioperative morbidity and mortality, and follow-up. All tumors were staged by the TNM classification system of the American Joint Committee for Cancer Staging.[15]

The date of esophagogastrectomy was defined as the starting point and the date of death or last follow-up as the end point. Operative mortality included all patients who died within 30 days of operation and those patients who died later but during the same hospitalization. Anastomotic leak was defined as disruption of the esophagogastric anastomosis identified by either radiographic contrast study, bedside oral grape juice test, or at the time of reoperation. Stricture was defined as anastomotic narrowing requiring endoscopic dilatation to relieve dysphagia. Continuous variables were reported as medians with interquartile range (IQR). Categorical variables were reported as proportions. The Mann-Whitney U, χ^2, and Fisher's exact tests were used for comparison between groups. Logistic regression analysis was performed to determine if an independent association existed between the type of anastomosis and outcomes, including leak rate, complications, and need for dilatation. A value of $P \leqslant .05$ was considered significant. Approval for this study was granted by the Mayo Foundation's Institutional Review Board.

Surgical Technique

The most common surgical approach used was Ivor Lewis, transhiatal, and, less frequently, extended esophagectomy (McKeown),[16,17] and our surgical techniques for these procedures have been described.[16,18–21] Other approaches included left thoracoabdominal and minimally invasive esophagogastrectomy. The latter consisted of thoracoscopic mobilization of the esophagus followed by laparoscopic mobilization of the stomach. The esophagus was then removed through a cervical incision, and a cervical esophagogastric anastomosis was then created.

Regardless of the surgical approach, preparation of the gastric conduit was similar and pyloromyotomy or pyloroplasty was routinely performed. The gastric conduit was constructed with multiple firings of a 3.5-mm linear stapler along the lesser gastric curvature. This longitudinal staple line was over sewn with running polypropylene or interrupted silk suture for all of the approaches except minimally invasive.

Both intrathoracic and cervical HSA were constructed in an end-to-side fashion using a variety of suturing techniques depending on the surgeon's preference. HSA were constructed with either

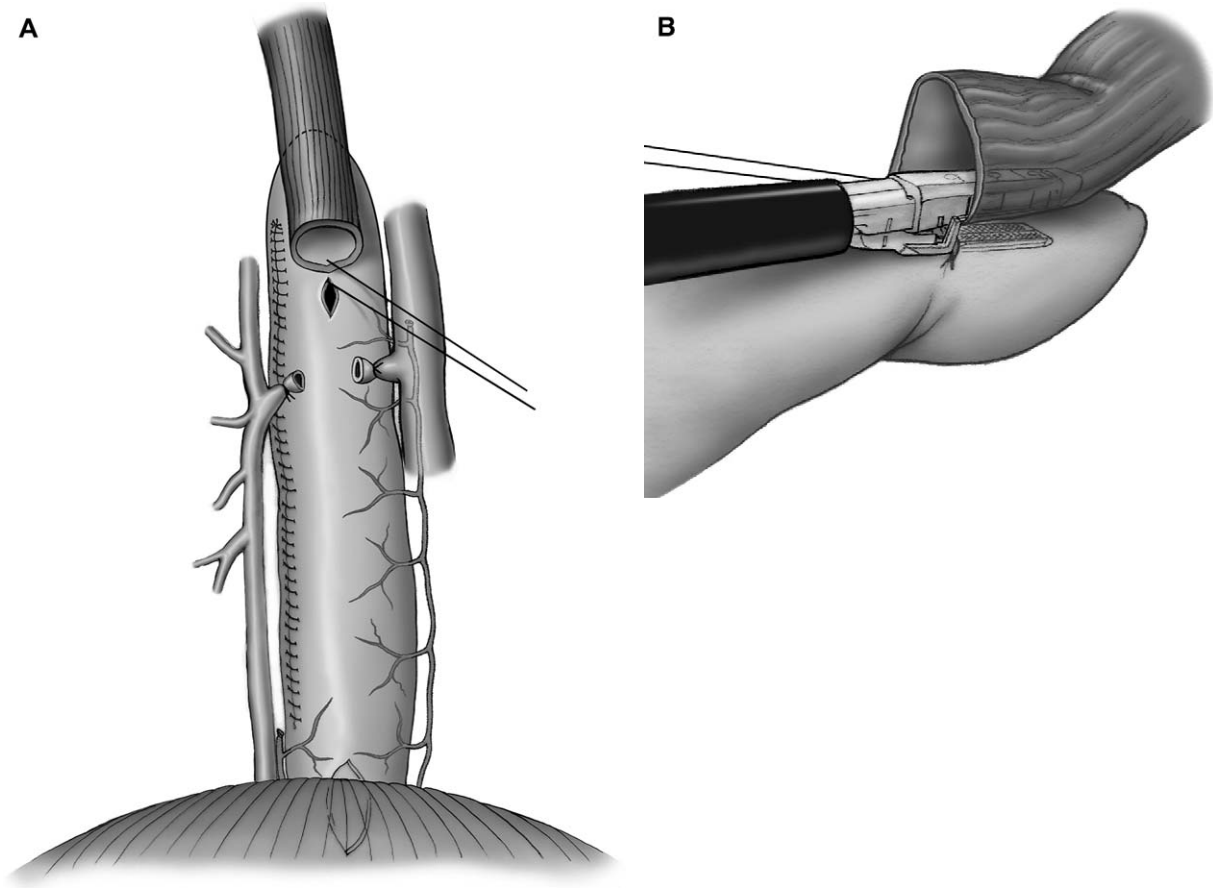

Fig. 2. Intrathoracic linear stapled esophagogastric anastomosis. An end-to-side anastomosis is constructed above the level of the divided azygos vein. (**A**) A longitudinal gastrotomy is made 5 cm inferior to tip of gastric fundus. A full-thickness 3-0 silk suture approximates distal esophagus to stomach. (**B**) A 3.5-mm endoscopic linear cutting stapler is used for the anastomosis. (**C**) Silk 3-0 reinforcing sutures are placed on either side of the esophagus and stomach. (**D**) The anterior esophagus and stomach are then closed transversely with an inner (mucosal) layer of running 3-0 absorbable suture and an outer layer of interrupted 3-0 silk suture. (**E**) The completed anastomosis with large triangulated posterior opening.

a single- or two-layer interrupted anastomosis of 3-0 silk or 3-0 polyglycolic acid suture.[2,16,18,20,21] Occasionally, multiple layers of 4-0 silk were used.[19]

Intrathoracic LSA were performed in an end-to-side fashion (Fig. 2, *A–E*). With the distal esophagus overlying the anterior wall of the stomach, a 1.0-cm longitudinal gastrotomy is made 5 cm inferior to the tip of the gastric fundus. A full-thickness 3-0 silk stay stitch approximates the esophageal mucosa and posterior esophageal wall to the gastric mucosa and anterior gastric wall (Fig. 2, *A*). A 3.5-mm endoscopic linear cutting stapler is used to create an end-to-side anastomosis (Fig. 2, *B*). Prior to removing the stapler, several silk reinforcing seromuscular sutures are placed between the esophagus and stomach on either side. The triangulated staple lines are inspected, and the anterior esophagus and gastrotomy are then approximated using an inner layer of running 3-0 absorbable suture and an outer layer of interrupted silk suture (Fig. 2, *D*). A nasogastric tube is then guided through the anastomosis and positioned above the pylorus.

Cervical LSA were created using one of two techniques. The first technique is similar to the intrathoracic LSA (Fig. 3, *A–D*). The second technique is a modification of the technique described by Collard and associates and results in a functional end-to-end anastomosis (Fig. 4, *A–E*).[22] The ends of the proximal stomach and the distal esophagus are brought laterally out of the cervical incision. A small gastrotomy is made, and the posterior wall of the stomach and esophagus apposed. A 4.5- to 5.0-cm side-to-side anastomosis is then created using a standard 3.5-mm linear cutting stapler. After inspecting the staple lines, the anterior wall of the esophagus and stomach are closed using a 4.8-mm transverse stapler. The transverse staple line is then oversewn with interrupted 3-0 silk suture. In both cervical LSA

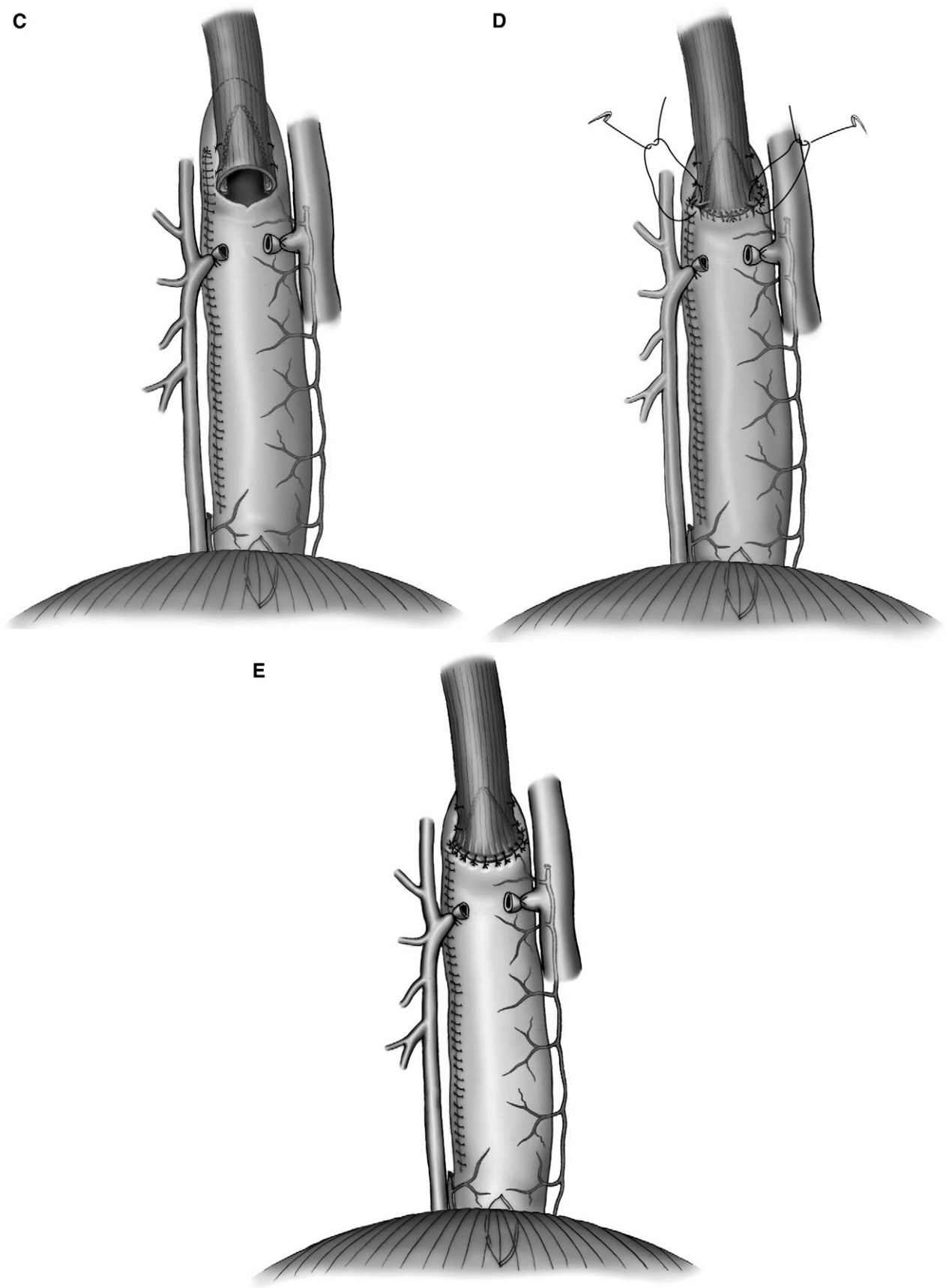

Fig. 2. *continued.*

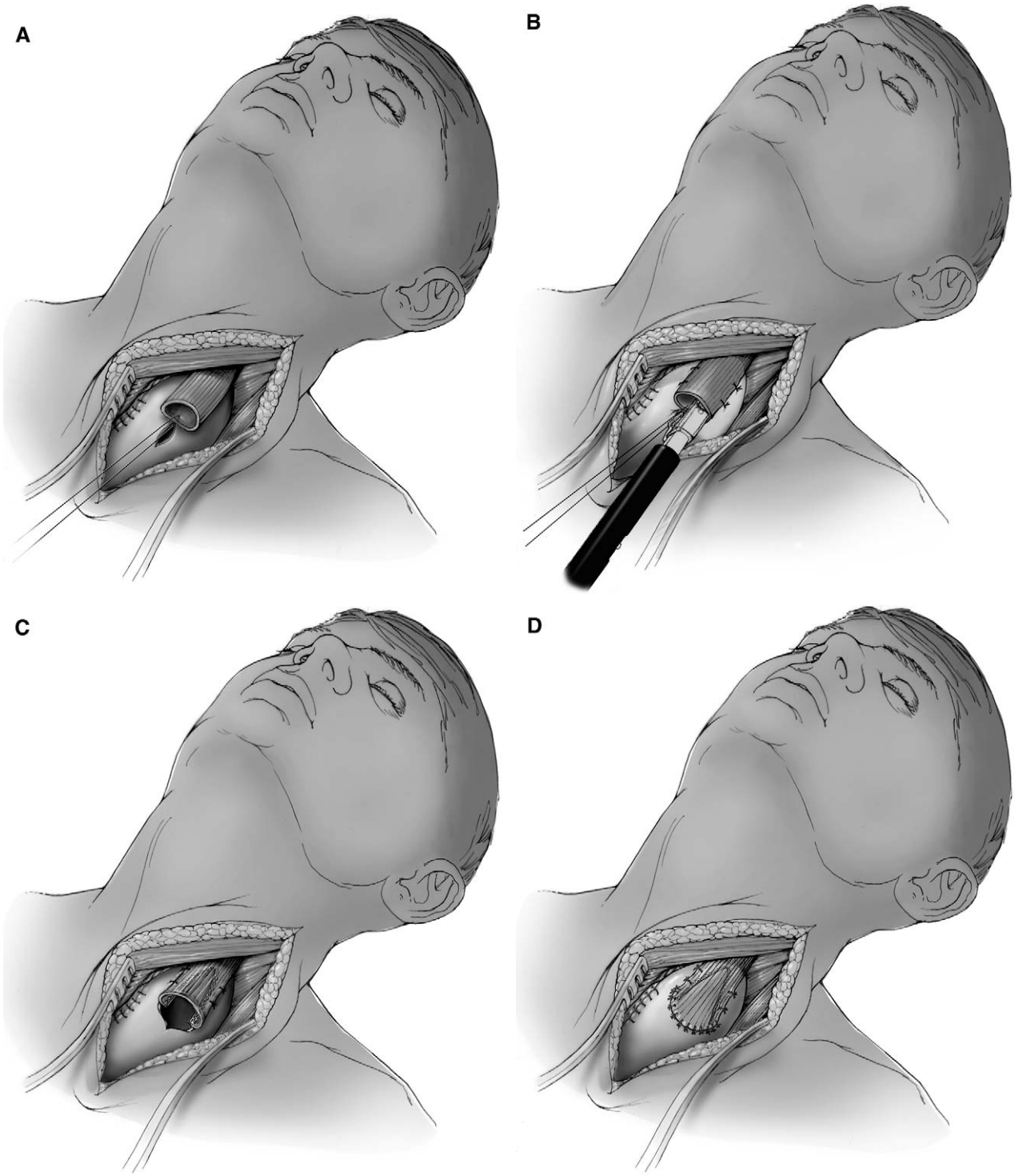

Fig. 3. Cervical linear stapled esophagogastric anastomosis. (**A**) A longitudinal gastrotomy is made 5 cm inferior to tip of gastric fundus. A full-thickness 3-0 silk suture approximates distal esophagus to stomach. (**B**) A 3.5-mm endoscopic linear cutting stapler is used for the anastomosis. (**C**) Silk 3-0 reinforcing sutures are placed on either side of the esophagus and stomach. The anterior esophagus and stomach are then closed transversely with an inner (mucosal) layer of running 3-0 absorbable suture and an outer layer of interrupted 3-0 silk suture. (**D**) The completed anastomosis with large triangulated posterior opening.

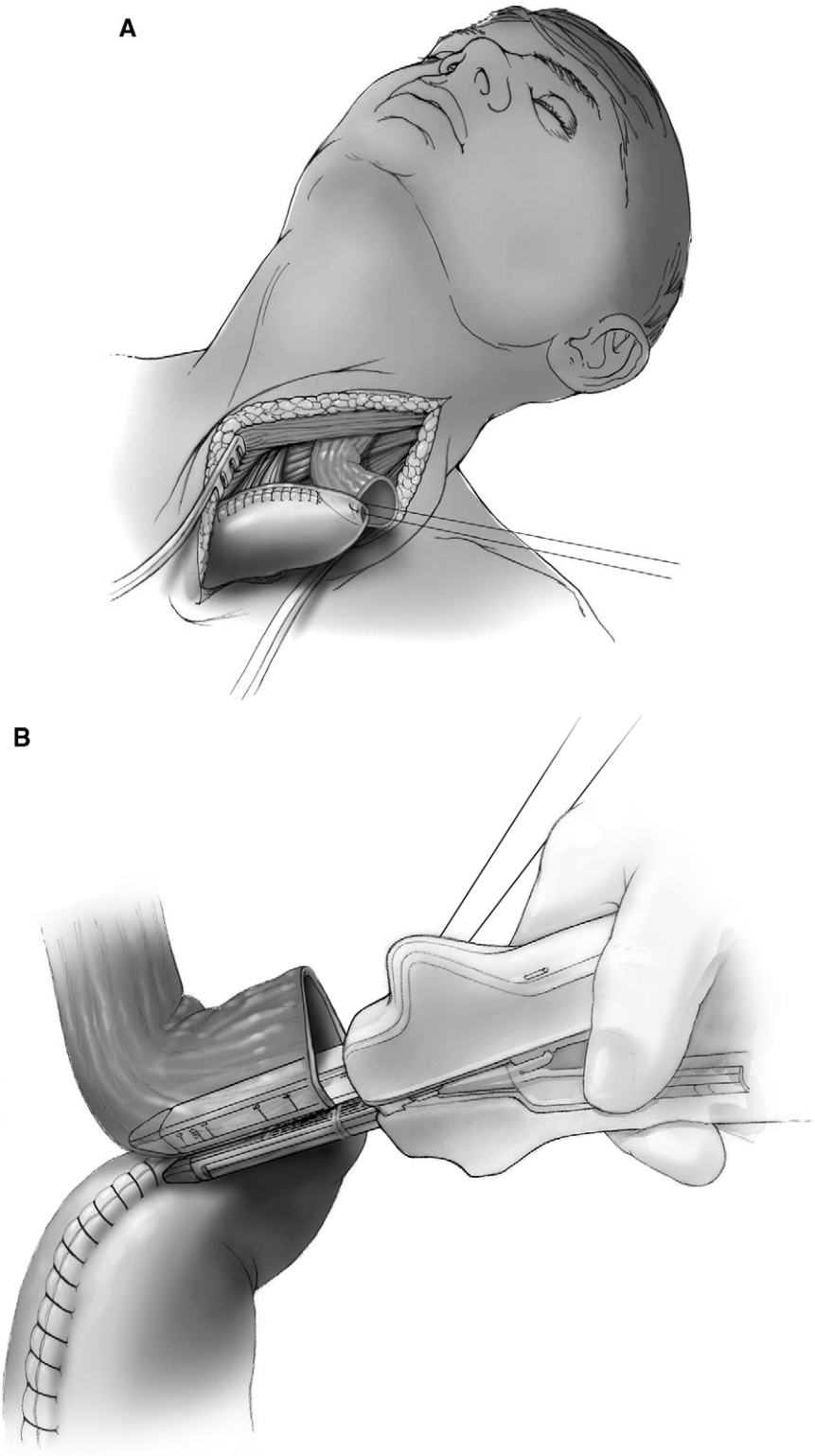

Fig. 4. Alternative cervical linear stapled end-to-end esophagogastric anastomosis. (**A**) The ends of the proximal stomach and distal esophagus are brought out through the cervical incision. A small gastrotomy is made in the tip of the gastric fundus. A full-thickness 3-0 silk suture approximates the esophagus and stomach. (**B**) A 3.5-mm standard linear cutting stapler is used to create a 4.5- to 5.0-cm side-to-side anastomosis. (**C**) Silk 3-0 sutures help approximate the esophagus and stomach, and a 4.5-mm transverse stapler is used to complete the anastomosis. This transverse staple line is oversewn with interrupted 3-0 silk suture.

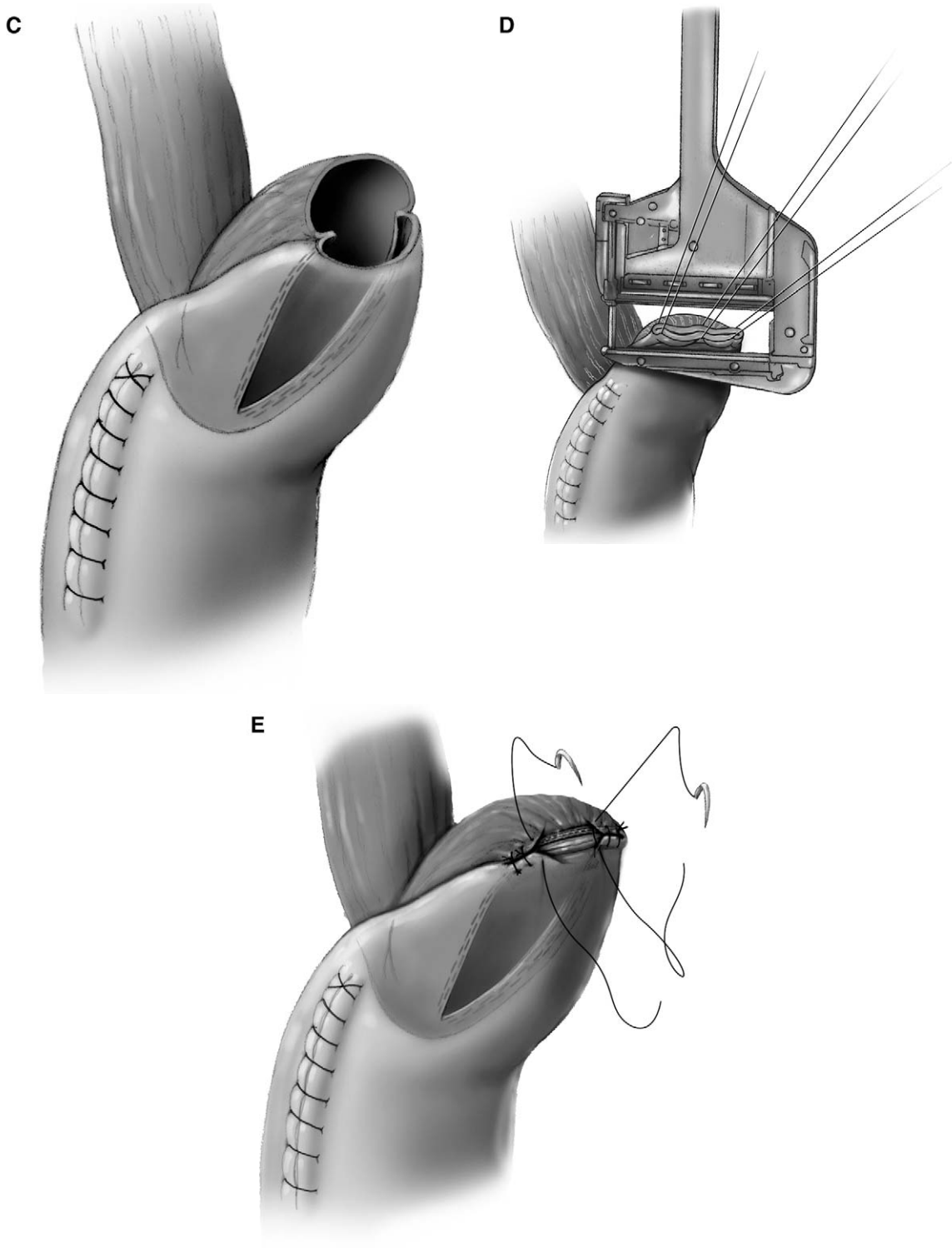

Fig. 4. *continued*

techniques, a nasogastric tube and cervical drainage catheters are used.

RESULTS

There were 280 patients (235 men and 45 women). Median age at the time of esophagogastrectomy was 65 years and ranged from 22 to 95 years. The indication for esophagogastrectomy was malignancy in 244 patients (87%), high-grade dysplasia in 22 (8%), and benign conditions in 14 (5%). Of the 244 patients with cancer, adenocarcinoma was present in 215 (88%) and squamous cell carcinoma was present in 29. The postsurgical stage was 0 in 42 patients (17.2%), stage I in 50 (20.5%), stage IIA in 55 (22.5%), Stage IIB in 35 (14.3%), stage III in 53 (21.7%), stage IVA in 6 (2.4%), and stage IVB in 3 (1.2%). One hundred seventeen patients (48%) received neoadjuvant therapy.

An Ivor Lewis esophagogastrectomy was done in 196 patients (70%), transhiatal in 58 (21%), left thoracoabdominal in 10 (3.6%), minimally invasive in 9 (3.2%), and extended (McKeown) in 7 (2.5%). HSA was done in 205 patients (73%) and LSA in 75 (27%) (Table 1). HSA was intrathoracic in 173 patients (62%) and cervical in 32 (11%). LSA was intrathoracic in 33 patients (12%) and cervical in 42 (15%). Overall, the anastomosis was intrathoracic in 206 patients (74%) and cervical in 74 (26%). The modified Collard anastomosis (Fig. 4) was used in 26 cervical anastomoses (62%).[22] Table 2 shows the comparison between the HSA and LSA groups. Significant differences were found with regard to age, use of neoadjuvant therapy, and intrathoracic anastomosis.

Follow-up was complete in all 280 patients and ranged from 8 days to 38 months (median, 9 months). Overall median hospitalization was 10 days and ranged from 5 to 98 days. The median hospitalization for LSA was 8 days (IQR, 7–14) and for HSA was 10 days (IQR, 8–13) (P = .01). Complications occurred in 62 patients (22%). Thirty-two patients had major complications without anastomotic leak, 22 had leak alone, and 8 had both (Table 3). Six patients died (mortality, 2.1%), 3 each with HSA and LSA.

Table 1. Location and Type of Esophagogastric Anastomoses

Anastomotic Location	HSA, n (%)	LSA, n (%)	Total, n (%)
Cervical	32 (11)	42 (15)	74 (26)
Intrathoracic	173 (62)	33 (12)	206 (74)
Total	205 (73)	75 (27)	280 (100)

HSA = hand-sewn anastomoses; LSA = linear stapled anastomoses.

Table 2. Comparison Between HSA and LSA Groups

	LSA	HSA	*P*-Value
Age (yr)	66.1 ± 10.9	62.5 ± 10.2	.01
Male gender	86.7%	82.9%	.45
Adenocarcinoma	76.0%	77.4%	.61
Neoadjuvant	21.9%	52.3%	.001
Intrathoracic anastomosis	44%	84.4%	.0001

HSA = hand-sewn anastomoses; LSA = linear stapled anastomoses.

Anastomotic leaks occurred in 30 patients (10.7%): 19 with intrathoracic anastomoses (9.2%) and 11 with cervical anastomoses (14.9%) (P = .013) (Table 4). The anastomotic leaks were HSA in 26 patients (86.7%) and LSA in 4 (13.3%). The leak rate for HSA was 12.7% (26 of 205) compared with only 5.3% (4 of 75) for LSA (P = .078). Because of the differences between the two groups, using logistic regression analysis when leak rate was adjusted for type of operation, gender, pathological diagnosis, surgeon, neoadjuvant therapy, and complications, the overall leak rate for HSA was significantly greater than that for LSA (P = .008).

Anastomotic leaks were aymptomatic in 17 patients (57%): 14 with intrathoracic anastomoses and 3 with cervical. All asymptomatic leaks were managed conservatively. The leaks in the remaining 13 patients (43%) were symptomatic and all required reoperation. These reoperations included primary repair in nine patients, drainage in two, and esophageal diversion in two. The rate of symptomatic

Table 3. Complications Following Esophagogastrectomy in 280 Patients

Complication	No. of Patients (%)
Anastomotic leak	30 (10.7)
Chyle leak	12 (4.3)
Respiratory failure requiring tracheostomy	9 (3.2)
Vocal cord paralysis requiring medialization	7 (2.5)
Empyema	6 (2.1)
Intra-abdominal abscess requiring drainage	3 (1.1)
Wound infection requiring debridement	2 (0.7)
Tracheal tear	1 (0.7)
Myocardial infarction requiring stenting	1 (0.4)
Pancreatitis requiring debridement	1 (0.4)
Pyloric obstruction	1 (0.4)
Incomplete resection	1 (0.4)
Hiatal hernia	1 (0.4)

Table 4. Comparison of Hand-Sewn (HSA) and Linear Stapled (LSA) Anastomoses

	HSA, n (%)	LSA, n (%)	*P*-Value	Adjusted *P*-Value*
Leak rate	26 (12.7)	4 (5.3)	.078	.008
Symptomatic leak rate	12 (5.8)	1 (1.3)	.195	—
Dilatation rate	70 (34)	11 (14.6)	.001	.002

*Denotes the effect of multiple variables on outcome based on logistic regression analysis.

anastomotic leak between HSA and LSA was not significant ($P = .195$).

Overall, 81 patients (28.9%) required esophageal dilatation (median, 2; range, 1–14). Dilatation was performed in 70 patients with HSA (34.1%) and in 11 with LSA (14.7%) ($P = .001$). Median time from esophagogastrectomy to dilatation was 82 days and ranged from 13 days to 3 years. Median time to dilatation was not significant for HSA or LSA ($P = .97$). Thirteen of the 30 patients (43%) with anastomtic leak required dilatation compared with 68 of 250 patients (27%) without leak ($P = .19$). When compared with LSA, patients with HSA were more likely to experience anastomotic leak or require dilatation; odds ratios and 95% confidence intervals were 5.35 (1.67–19.27) and 3.58 (1.66–8.34), respectively.

DISCUSSION

A successful anastomosis is essential to the favorable outcome of esophagogastrectomy. Our previous esophagogastrectomy series using primarily HSA have shown anastomotic leak rates ranging from 3.2% to 13%.[1,2,8,9,14,23] These results compare favorably to the 12%–23% leak rate reported by others.[24–27] Furthermore, Muller and associates[24] demonstrated similar anastomotic leak rates regardless of whether the HSA was performed in one layer or two layers or with a circular stapling device. In a meta-analysis using five randomized controlled trials, Urschel and colleagues[6] also demonstrated similar leak rates for HSA and circular stapled anastomosis. Their analysis, however, did not account for the sizes of the circular stapling devices, techniques of HSA, and location of the anastomoses. It is possible that the final diameter of HSA was not appreciably different from smaller or medium-sized circular stapled anastomoses, thus accounting for the similarity in stricture rates. We have not favored the circular stapling device for esophagogastric anastomoses because of the reported higher stricture rate.[5,28] Four of the five trials in the meta-analysis review included information regarding duration of operation and time to anastomosis completion. These authors found that HSA anastomoses took longer to complete and that this was statistically significant in two of the studies; however, the duration of operation was not significantly different in three of four studies.[6] We did not include data about operative time or anastomotic time; however, it is our impression that LSA requires less time to construct.

Anastomotic leak following esophagogastrectomy is a known risk factor for development of anastomotic stricture, and cervical anastomotic stricture has been reported to occur in almost 50% of cervical anastomotic leaks.[25] While patients rarely die from these anastomotic strictures, we have demonstrated that these leaks and subsequent strictures have adversely affected quality of life.[8,14]

LSA techniques are clearly different from circular stapling techniques. The triangulated posterior opening created by the linear stapler combined with the transverse anterior closure of the esophagus and stomach creates a secure large opening. It is possible that the linear stapler is less traumatic and more uniform than the suturing required for HSA. It is also possible that the large triangulated opening created with LSA results in decreased early anastomotic obstruction compared with both HSA and circular stapling techniques, resulting in decreased anastomotic leakage and subsequent decreased long-term stricture formation. Our comparison between the two techniques has to be tempered because this is a retrospective review. A randomized trial would be the ideal method to compare both anastomotic techniques; however, this would be nearly impossible to perform.

Our techniques of LSA are somewhat different from those of other authors in that the anterior gastrotomy is created in a longitudinal fashion.[22,25,29] After creation of the posterior triangulated stapled opening, a size discrepancy often exists between the anterior esophagus and anterior stomach, and the longitudinal gastrotomy can be lengthened, if necessary, to allow for easier suturing of the anterior esophagus with the anterior stomach. For the modified Collard technique, we have found no problem using the transverse noncutting stapler for closure of the esophagotomy and gastrotomy. This transverse staple line is then oversewn with interrupted silk suture.

CONCLUSION

LSA is safe and associated with both a significantly lower leak rate and the need for dilatation compared

with HSA. This nonrandomized series suggests that LSA is the preferred technique regardless of anastomotic location.

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Discussion

Dr. Jeffrey Peters (Rochester, NY): Very nicely presented, Dr. Behzadi. I particularly congratulate you on the quality of your illustrations, they were beautiful, and I also thank the Society and the moderators for the privilege of this discussion. The clinical care and outcome of patients undergoing

esophagogastrectomy has improved markedly in the last 50 years. Mortality has steadily declined from what was once one in every two to three patients to now one or two in every 100 patients. The use of intensive care units, bronchoscopy, epidural analgesia, and probably a healthier patient population all have had significant impact. Improvements in the anastomosis, however, and its consequences have evolved more slowly. Anastomotic leak continues to occur in 10–15% of patients, as you saw in this manuscript, despite efforts to lessen its incidence, and strictures requiring dilation continue to occur in 30–40%.

Comparison of stapled versus hand-sewn anastomoses has been around for a while, but until recently, most have focused on circular stapling techniques. Circular staplers have been shown to provide little advantage over hand-sewn anastomoses and, in fact, may increase stricture formation. The linear stapling techniques emerged over the last decade, particularly with the advent of the laparoscopic instrumentation, as you pointed out, and have been adopted by several centers, including now the Mayo Clinic. In this large series of patients, hand-sewn anastomoses were five times more likely to leak and three and one-half times more likely to require dilation. Compelling data indeed. I have several questions.

Is there a significant learning curve here? And perhaps can you comment on some of the technical nuances, such as parallel staple lines and the length necessary for both the gastric graft and esophageal remnant? Several centers, including our own, have tried and abandoned these linear stapling techniques. Most have found that for cervical anastomosis, at least, it requires a greater length of the gastric fundus in the neck. Has this been your experience, and have you chosen not to pursue the stapled anastomoses for certain technical reasons in a minority of your patients?

Your data reflect the fact that the majority of hand-sewn anastomoses were intrathoracic and the stapled ones were cervical, something like 80:20. Do you think the location of the anastomosis may have impacted your data and the differences you observed?

And finally, the anastomotic leak and stricture formation have been thought to be primarily driven by the relative ischemia of the proximal gastric fundus, not necessarily by technical issues. Do you, first, accept this premise, and if you do, can you conjecture as to why a stapled anastomosis might be better?

This is a well-done and provocative paper thatwill give many of us pause and prompt consideration of this alternative technique.

Dr. Behzadi: Thank you very much, Dr. Peters, for your comments. As for the learning curve, we did not find it to be very challenging, perhaps because we all went through general surgery training where the use of staplers is now quite frequent and a part of basic training.

As I mentioned in the presentation, it is only when we don't have an adequate length of esophagus that we do not use a linear stapled anastomosis and in this situation utilize a hand-sewn anastomosis. It is true that with the modified Collard anastomosis additional cervical esophageal length is necessary. Importantly, the modified Collard anastomosis, however, still lies low in the neck or near the uppermost part of the thoracic inlet. In all cases, gastric conduit length is rarely a problem.

As far as ischemia goes, we are very careful in the mobilization and transposition of the gastric conduit. Stapling as opposed to hand-sewing the anastomosis may be less traumatic on the tissues and also provide a more uniform final anastomosis. Additionally, the wide open triangulated anastomosis may lead to less obstruction in the immediate perioperative period and in turn decrease the incidence of anastomotic leaks.

As for the location of the anastomosis, we agree with you that most of the anastomoses were in the chest. This is because of our preference over the years for the Ivor Lewis esophagogastrectomy procedure for the management of esophageal cancers. In order to gain experience with the linear stapled technique, we started using this technique in the neck, where we all know that anastomotic leaks can be better tolerated. Once we were convinced that the leak rate for the stapled anastomosis in the neck was no higher, we progressed to using this stapled anastomotic technique in the chest. Ultimately, we showed that the leak rate and stricture rate for the linear stapled anastomosis was significantly less than for the hand-sewn anastomosis.

Dr. Keith Lillemoe (Indianapolis, IN): This is a nice study but as a retrospective study it is confounded by so many variables that cannot be controlled. I would challenge your high-volume group to really answer this important question properly by completing a prospective randomized trial. You have the numbers, you have a pretty dramatic expectation of the results. I don't think you would need a lot of patients to power it properly. It is begging for a prospective randomized trial, and I challenge the Mayo Clinic to step up and do this it.

Dr. Behzadi: There has been a practice change at the Mayo Clinic based on the introduction of the stapler anastomosis. In fact, all of our surgeons at this time perform this stapled anastomosis. So doing a randomized study would be challenging, as everyone feels that this is the way to go.

Dr. Francis Nichols (Rochester, MN): We will take that information back to Rochester. We have actually thought about a randomized trial, but we have been so impressed with the results using the linear stapler that we are having trouble justifying that trial. Whereas we previously almost exclusively hand-sewed the anastomosis, we now routinely use the linear stapled anastomosis in both the chest and neck. With the hand-sewn technique, we knew that our leak rate was within an acceptable range and lower than many series. Nonetheless, like other series, stricture formation was a frustrating problem. By stapling the anastomosis with the linear stapler and creating a triangulated anastomotic opening, we hoped to decrease the anastomotic stricture rate. Anastomotic strictures often require repetitive dilatations, and they are frustrating to the patient and physician. It must not be forgotten that there always is a risk of perforation with dilatation. We previously have shown that anastomotic strictures measureably decreased quality of life.

The endoscopic linear staplers make doing the stapled anastomosis in the chest much easier. I think the staplers lead to less anastomotic trauma, less edema, and in turn a decreased stricture rate. Whereas we used to send anywhere from 10–30% of our patients for dilatation, it has now become a rare event when the anastomosis is stapled. Importantly, the leak rate hasn't increased and in fact it appears to have gone down.

Thank you for allowing us to present our results, and I will take your comments back home with me.

Dr. Andrew Warshaw (Boston, MA): I may be missing something, but your stapled anastomosis has at least half of it as hand-sewn, so why do you call it a stapled anastomosis?

Dr. Behzadi: There are various ways of describing the stapled anastomosis. For a complete circular stapled anastomosis done with the circular stapling device, even then a gastrotomy for the introduction of the stapler needs closure. This closure may be stapled or hand-sewn. The modified Collard anastomosis when done as we described is entirely stapled, although we do oversew the transverse staple line with interrupted silk suture. Finally, there is the end-to-side esophagogastric anastomosis that uses a linear stapler for the posterior wall. While the anterior wall can be closed with a stapler, we have generally found it easier to complete this portion in a hand-sewn fashion. What we are describing in all of our stapled cases is the creation of a large stapled triangulated opening that appears to be resistant to stricture formation and less prone to leak. This is in contrast to the circular stapler or an entirely hand-sewn anastomosis, which while not stapled, most often ends up being circular in shape and about the same final diameter as the circular stapled anastomosis. It is these ultimately smaller circular anastomoses that seem to be prone to stricture formation.

Forty-Eight-Hour pH Monitoring Increases Sensitivity in Detecting Abnormal Esophageal Acid Exposure

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Ambulatory 24-hour esophageal pH measurement is the standard for detecting abnormal esophageal acid exposure (AEAE), but it has a false negative rate of 15% to 30%. Wireless 48-hour pH monitoring (Bravo; Medtronic, Shoreview, MN) may allow more accurate detection of AEAE versus 24-hour pH monitoring. Forty-eight-hour wireless data were reviewed from 209 patients at three different tertiary care referral centers between 2003 and 2005. Manometric or endoscopic determination of the lower esophageal sphincter helped place the Bravo probe 5 to 6 cm above the lower esophageal sphincter. A total of 190 studies in 186 patients had sufficiently accurate data. There were 114 women and 72 men with an average age of 51 years. AEAE was defined by a Johnson-DeMeester score greater than 14.7 and was obtained in 115 of 190 studies (61%). Only 64 of 115 patients (56%) demonstrated AEAE for both days of the study, whereas 51 of 115 patients (44%) demonstrated AEAE in a single 24-hour period. There was no difference in the prevalence of AEAE on day 1 versus day 2 only (26% vs. 18%, $P = .26$). Compared with 24-hour alone data, 48-hour data showed 22% more patients with AEAE. Frequent day-to-day variability in patients with AEAE may be missed by a single 24-hour pH test. Forty-eight-hour pH testing may increase detection accuracy and sensitivity for AEAE by as much as 22%. (J GASTROINTEST SURG 2005;9:1043–1052) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Gastroesophageal reflux, monitoring, ambulatory, gastric acidity determination

Ambulatory 24-hour esophageal pH monitoring has been found to be useful in evaluating and treating patients with established or suspected gastroesophageal reflux disease (GERD). Previous studies have revealed that it is both a sensitive and specific test in the diagnosis of GERD.[1,2] The current technique involves passing a small-caliber probe transnasally into the esophagus positioned 5 cm proximal to the manometrically determined upper border of the lower esophageal sphincter (LES). The probe is fixed to the nose and attached to a recording unit worn by the patient. After 24 hours, the probe is removed and the collected data for this period are transferred to a computer for analysis.

Despite this established methodology for ambulatory 24-hour pH monitoring, there are a number of limitations with this system. The transnasal catheter may be embarrassing for many patients, causing them to remain at home and avoid their normal daily activities.[3] Discomfort from the transnasal catheter or dysphagia has been established to result in abnormal eating, drinking, and sleeping patterns.[4] These limitations to a patient's established routine may reduce the likelihood of reflux events that allow one to document pathologic intraesophageal acid exposure and thus diagnose GERD. Thus, the results from this test may not reflect the true severity of the disease, and thereby underestimate the prevalence of GERD.[4] This is suggested by a study in those with positive 24-hour pH study results, in which 16% of patients had negative test results on a follow-up 24-hour pH study within 10 days.[5] This day-to-day variability in some patients

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with GERD can be missed by using only a 24-hour recording period.

Longer intraesophageal pH monitoring is now available using the Bravo probe (Medtronic, Shoreview, MN), a novel 48-hour pH measurement device, and it has shown promising results. The device is implanted in the mucosa of the esophagus to a position determined manometrically or endoscopically that is 5 to 6 cm above the gastroesophageal junction. The capsule relays information by radiofrequency to a portable receiver the patient wears on his or her waist or places on the bedside table while sleeping. There are several inherent advantages of such a wireless implantable system. It eliminates the unsightly transnasal probe that may limit daily normal activities. Patients do not experience nasal discomfort and have less dysphagia, and therefore can more easily resume a normal diet after placement.

Preliminary data demonstrated that the results of this 48-hour wireless probe are comparable to an ambulatory 24-hour pH study.[6] However, further study has revealed that the Bravo probe may be able to detect patients with abnormal esophageal acid exposure (AEAE) that the ambulatory 24-hour pH probe would otherwise miss because of the extended recording time.[6] We hypothesized that the additional monitoring period available, and the increased likelihood of more normal activity and dietary behavior achievable with this device, would improve the detection of GERD versus that obtained with a traditional 24-hour tube-based system. Ideally this would be proven by a randomized trial comparing the two devices, but such a study would be difficult to perform given the discomfort associated with the tube system. Therefore the aim of this study was to retrospectively evaluate and assess multi-institutional Bravo data in terms of its ability to detect AEAE with the extended data recording up to 48 hours and contrast that with the data obtained in the first 48 hours as a surrogate for the tube-based 24-hour system. This approach actually is bias against the Bravo device because it does not take into account the discomfort and altered habits that may minimize GERD detection further with a tube-based system, if actually used. Thus any differences detected are likely less than those that would be demonstrated in a randomized trial.

METHODS

Patient Selection

After institutional review board approval was obtained, we performed a retrospective chart review of all 48-hour pH studies performed at three medical centers (Oregon Health and Science University, Legacy Health System, and Swedish Medical Center) between 2003 and 2005. To be included in the analysis we required that (1) patients were aged more than 18 years, and that (2) patients were being evaluated for GERD. We included patients evaluated by wireless 48-hour pH monitoring with typical and/or atypical symptoms of GERD, recurrent GERD symptoms after surgical or endoscopic antireflux procedure, or persistent GERD symptoms on medical therapy. The 48-hour pH examination was offered on the basis of availability, inability to tolerate standard ambulatory 24-hour pH testing, or indications in which a 48-hour examination was believed to be indicated.

Before the 48-hour wireless test was performed, patients were instructed to discontinue all antacid and antisecretory medications for a minimum of 7 days at Oregon Health and Science University and a minimum of 5 days at Legacy Health System and Swedish Medical Center. The only exception occurred in patients being evaluated for whom referring physicians specifically requested the study be performed on medications. Diet restriction included nothing by mouth at least 6 hours before procedure. No diet modification was recommended during the study.

Procedure

The Bravo device was attached to the esophageal mucosa in a location determined by either manometric or endoscopic measures at 5 to 6 cm above the LES. If the procedure was endoscopically performed, conscious sedation was given to the patient in the form of midazolam and fentanyl. The squamocolumnar junction was then visualized, and the probe was fixed to the esophageal mucosa 5 to 6 cm above this point. If the probe was placed manometrically, no sedation was given. The upper border of the LES was identified, and the probe was passed transorally until (11 cm proximal to the manometrically determined upper border of the LES to account for the usual 5 cm difference in length of this site between nasal and oral placement) it was 5 to 6 cm above this point. Proper functioning of the Bravo probe was confirmed by a reading of pH greater than 4 immediately after placement.

If the patient had the endoscopic appearance of Barrett's esophagus, identification of the proximal gastric folds was used to estimate the location of the squamocolumnar junction. Alternatively, if the patient had a large hiatal hernia, the proximal gastric folds were used to estimate the location of the squamocolumnar junction; the site for implantation of

the probe was 6 cm proximal to the proximal gastric folds.

Data Collection

During monitoring, patients were encouraged to resume their usual daily routine of meals and activity. Reflux symptoms were recorded by depressing a button on the Bravo unit, marking the time at which it occurred. A diary was kept for recording meals, medication, and patient position. Previous antisecretory medications were resumed after the 48-hour monitoring period was complete.

Information was transmitted to the portable receiver, which was required to be within 3 to 5 feet of the patient to record accurate data. An exception was made during bathing, in which the patient was instructed to keep the unit within 5 feet.

After 48 hours, the patients returned the recording unit and the record sheet to the gastrointestinal laboratory. The information was downloaded to a personal computer for data analysis. Bravo data were then collated along with clinical patient information and entered on a Microsoft Excel (Redmond, WA) spreadsheet to allow comparative analysis.

Positive Bravo Test

We arbitrarily chose to define AEAE with the Johnson-DeMeester scoring system using a threshold of greater than 14.7.[7] The Johnson-DeMeester scoring system has been widely used in ambulatory 24-hour pH testing as a quantitative value for detecting the presence of GERD. Recently, DeMeester and colleagues validated this scoring system for the Bravo probe by comparing the original non-GERD 24-hour data with Bravo 48-hour data obtained in patients without GERD. They discovered that the total Johnson-DeMeester score was not significantly different, but did identify that the percentage of total time that the pH was less than 4 and the number of long reflux episodes were greater in those with wireless 48-hour pH data versus conventional controls with 24-hour pH data.[8]

In addition, Pandolfino et al.[9] reported that the percentage of total time that the pH was less than 4 in patients with GERD at the 95th percentile was more than 5.3%, higher than what is traditionally used at a cutoff of more than 4%. Therefore, we also decided to run a separate analysis using this different criterion for defining AEAE and examine the results found from both definitions of AEAE.

All pH tracings were examined, and studies in which the pH was persistently less than 4 for 60 minutes and then normalized for the remainder of the trial were excluded. This finding indicates dislodgement of the probe and passage through the stomach into the small bowel. Also if there were less than 18 hours of data on either of the two 24-hour periods, these studies were considered insufficient for analysis.

Statistical Analysis

Statistical analysis software SPSS 13.0 (SPSS Inc., Chicago, IL) and Microsoft Excel were used for calculations. Values from pH testing were not normally distributed; therefore median values were calculated, and nonparametric tests were used for detecting significance. Correlations between continuous data were made with Pearson's correlation coefficient. Differences in AEAE prevalence between days were compared using McNemar's test. The Wilcoxon signed-rank test was used to compare median values between 2 days of Bravo data. A P value less than .05 was considered statistically significant.

RESULTS

Patients and Bravo Studies

There were 209 patients who had Bravo probes placed. Five patients had the test performed twice; thus, 213 studies were available for analysis. Placement was performed successfully initially in all but one patient. One patient had an extremely severe gag reflex, preventing placement of the Bravo. This patient underwent transnasal ambulatory 24-hour pH monitoring instead and was not included in this analysis; 190 recordings from 186 patients were obtained after excluding those with less than 18 hours of data on at least one of the two 24-hour periods (18 patients), and those in whom there was evidence of premature dislodgement (five patients). There were 72 males (39%) and 114 females (61%) with a mean age of 51 years in this remaining group of patients. Complications were generally mild with most patients noting a foreign body sensation. Only two patients reported sufficient chest pain. All capsules were presumed to have dislodged within 2 weeks (no symptoms persisted beyond this point), and none had to be retrieved endoscopically.

Analysis with Johnson-DeMeester Score

When a Johnson-DeMeester score greater than 14.7 was applied to the results from the 48-hour wireless study, 115 of 190 studies (61%) were positive for AEAE. Of the positive 48-hour wireless studies, 30 were positive on day 1 only, 21 were positive on day 2 only, and 64 were positive on both days 1 and 2 (Fig. 1, *A*). If the 48-hour wireless test was

positive on a single day, 30 of 51 (59%) occurred on day 1, and 21 of 51 (41%) occurred on day 2. There was no significant difference identified between the prevalence of a positive 48-hour wireless study on day 1 versus day 2 of testing ($P = .26$) (Table 1, *A*). The median difference in Johnson-DeMeester scores between one positive day and one negative day was 17.8 (interquartile range 11.5–27.7).

The odds ratio of having AEAE on day 2 in the presence of AEAE on day 1 was 7.6 (95% confidence interval 4.0–14.6). The negative predictive value of 24-hour data alone was 78%. Had only one 24-hour period of testing been performed, 94 patients would have been detected, with 21 patients (22%) being misclassified as normal (false-negative tests).

Analysis with Pandolfino Criteria

If a positive 48-hour wireless pH test for AEAE was defined by the percentage of total time the pH was less than 4 for 5.3% of a 24-hour period, 103 of 190 (54%) of studies were positive. This threshold resulted in a decrease in the overall number of patients with AEAE. There were 28 positive on day 1 only, 19 positive on day 2 only, and 56 positive on both days (Fig. 1, *B*). The median difference between the percentage of total time the pH was less than 4 for one positive day and one negative day was 6.6% (interquartile range 4.0–8.9).

There was no significant difference between the prevalence of a positive Bravo study result on day 1 versus day 2 ($P = .24$) (Table 1, *B*). The odds ratio of having a positive Bravo test result on the second day if the first day was positive was 9.2 (95% confidence interval 4.7–17.9). The negative predictive value increased slightly to 82%. If the recording was stopped after only a single 24-hour period, 84 patients with AEAE would have been detected. By extending this to 48 hours, another 19 patients were discovered, increasing the number detected by 23%. Therefore, regardless of the threshold measure used, there were similar increases in the number detected by extended recording to 48 hours between the two methods used for analysis (Table 2).

The correlation between the Johnson-DeMeester score and the percentage of total time the pH was less than 4 was carried out over all values (Fig. 2). There was a high degree of correlation between the two threshold values ($r = 0.96$, $P < .001$). The best correlation occurred in the normal range, whereas a larger deviation occurred at higher values.

Day-to-Day Variability

The large number of patients who showed AEAE on only 1 of 2 days highlights the day-to-day variability in distal esophageal acid exposure in patients with GERD. The correlation between 2 consecutive days of data was relatively poor ($r = 0.6$) (Fig. 3). However, when patients were considered who had negative 48-hour wireless pH results for AEAE, the interday difference was a median DeMeester difference of 2.0 (interquartile range 0.4–4.1). The relevance of these findings suggests that in patients without AEAE, the wireless 48-hour probe has little variance over the 2 days.

To ensure that these findings were not confounded by the method of placement (endoscopic vs. manometric) or length of time that proton-pump inhibitor therapy was stopped before testing (5 days vs. 7 days), we performed a separate analysis directly comparing these two groups. Placement by

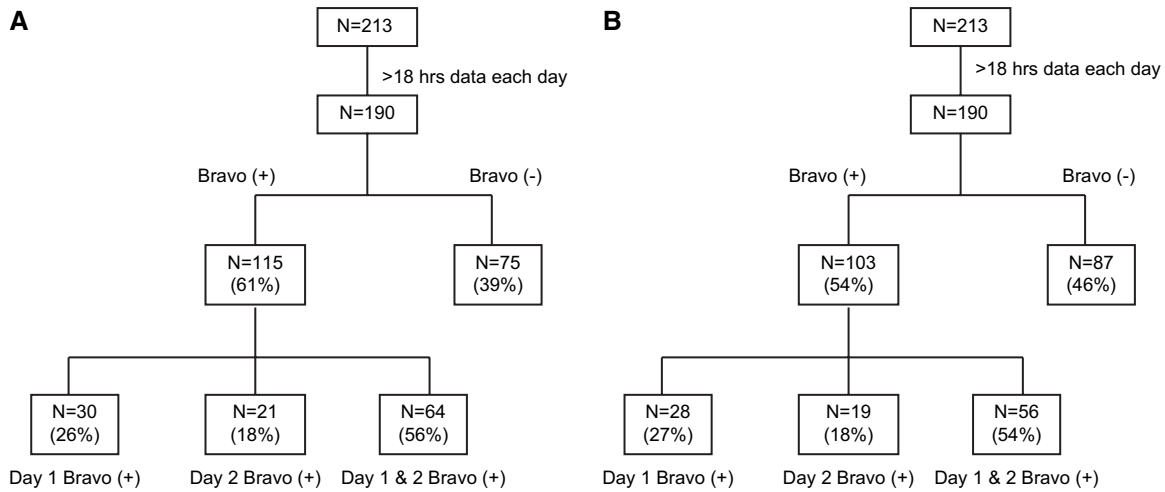

Fig. 1. (**A**) Bravo results defined by a Johnson-DeMeester score greater than 14.7. (**B**) Bravo results defined by a threshold more than 5.3% for percentage of total time pH was less than 4.

Table 1. Crosstabulation results from Bravo tests Day 1 versus Day 2

(A) DeMeester score >14.7 for Bravo (+)

Johnson-DeMeester score more than 14.7		Bravo Day 2 Negative	Bravo Day 2 Positive	Total
Bravo Day 1	Negative	75	21	96
	Positive	30	66	96
Total		105	87	192

(B) % total pH <4 more than 5.3% for Bravo (+)

% total pH <4 more than 5.3%		Bravo Day 2 Negative	Bravo Day 2 Positive	Total
Bravo Day 1	Negative	87	19	106
	Positive	27	59	86
Total		114	78	192

endoscopic or manometric means did not significantly change the occurrence of AEAE on day 1 or 2 (Table 3, *A*). The period of time that proton-pump inhibitor therapy was stopped (5 days vs. 7 days) did not have any influence on the detection of AEAE (Table 3, *B*).

DISCUSSION

The diagnosis of GERD is a clinical diagnosis made with a number of factors that include both symptoms and objective evaluation. Although there is no consensus definition of GERD, many experts believe that GERD is "the abnormal exposure of the esophagus to gastric juice regardless of symptoms or complications."[10] To quantify the amount of exposure of the esophagus to gastric refluxate, ambulatory 24-hour pH testing was developed. By measuring various parameters of esophageal acid exposure, Johnson and DeMeester[7] were able to develop a scoring system for the diagnosis of GERD. This scoring system was based on six parameters of the pH test results: percentage of total time pH was less than 4, percentage of upright time pH was less than 4, percentage of supine time pH was less than 4, number of reflux episodes, number of episodes with pH less than 4 for more than 5 minutes, and the period of the longest single acid exposure episode. Each of the parameters undergoes a weighting based on the parameter's standard deviation, and then all are added together. After completing 24-hour pH testing in 50 healthy controls, DeMeester and colleagues showed that a score greater than 14.7 exceeded the 95th percentile of medical student volunteers. Values greater than this were thought to be diagnostic for GERD. In 1992, Jamieson et al.[1] discovered that the best indicators for GERD were the composite (Johnson-DeMeester) score and the percentage of total time the pH was less than 4. Although many physicians consider the percentage of total time the pH was less than 4 as the best indicator for pathologic esophageal acid exposure, many still use the Johnson-DeMeester score as part of their evaluation.

We demonstrated in this study that the Johnson-DeMeester score is a reliable indicator for GERD given the strong correlation found between the percentage of total time the pH was less than 4 and this score. It is worthwhile to note in this study that the Johnson-DeMeester score seemed to be a more sensitive test for AEAE. It is unknown whether this observation should influence which analysis clinicians should use to interpret esophageal pH data, and we cannot speculate on this at this time. In addition, no data exist evaluating the results of medical, endoscopic, or surgical therapy in patients found to have GERD by using the wireless 48-hour pH results.

What is evident from these data is that quantifying a patient's esophageal acid exposure on a single 24-hour time period alone may be falsely negative

Table 2. Changes in detection of AEAE based on two separate selection criteria schemes

		Percentage of time pH <4 more than 5.3% No AEAE	Day 1(+), Day 2(−)	Day 1(−), Day 2(+)	Day 1(+), Day 2(+)	Total
Johnson-DeMeester score > 14.7	No AEAE	74	1	0	0	75
	Day 1(+), Day 2(−)	**7**	23	0	0	30
	Day 1(−), Day 2(+)	**5**	0	16	0	21
	Day 1(+), Day 2(+)	**1**	**4**	**3**	56	64
Total		87	28	19	56	190

Highlighted numbers represent the additional patients with AEAE who are detected by using the Johnson-DeMeester scoring system.
AEAE = abnormal esophageal acid exposure.

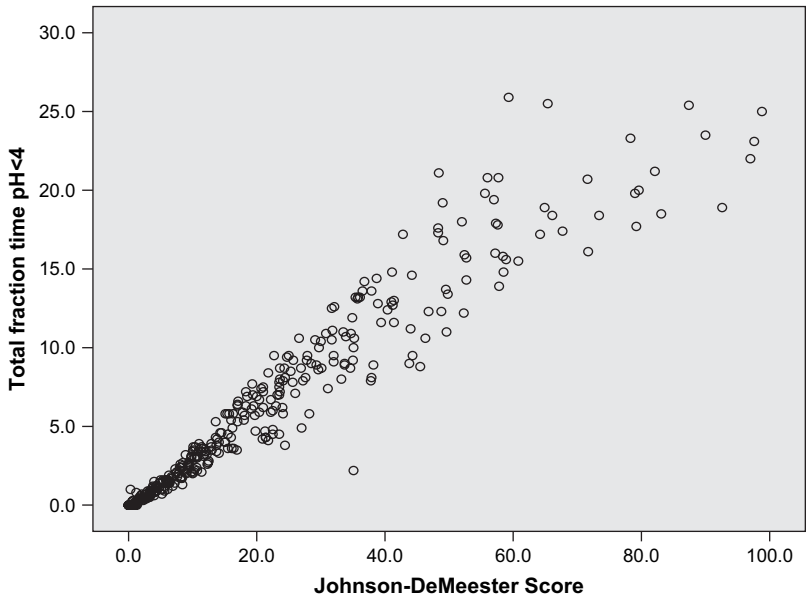

Fig. 2. All values obtained in 190 studies over 48 hours; $r = 0.96$, $P = .001$.

even without the confounding variables introduced with the catheter-based approach. By using traditional techniques, one recent study reported discordant results in 6 of 22 patients when tested with 24-hour pH monitoring 6 weeks apart.[11] Other authors have reported similar findings and suggest that day-to-day variability in AEAE is not an uncommon phenomenon.[5,12] In fact, our data suggest that only 56% of patients with AEAE demonstrate continuous 48-hour abnormalities in esophageal acid exposure. These results are lower than suggested by a small early study in which 25 of 37 patients with GERD (68%) exhibited 48-hour AEAE.[12] Regardless of the true variation between 24-hour periods with this technique, the significance of these findings in these two studies indicates that our ability to detect AEAE on 24-hour pH data alone may be insufficient.

If we had not recorded the second 24-hour period of data in the Bravo probe group, we would have misdiagnosed 22% of patients who had AEAE. In other words, the negative predictive value of a 24-hour test alone is 78%, similar to what was found in a previous study using wireless 48-hour probes.[6] However, the main advantage of extending the recording time may not be just in the detection of AEAE, but also in the ability to correlate symptoms with reflux events. Prakash and Clouse[6] demonstrated that the largest gains in detection of GERD by 48-hour monitoring may be in improved determination of symptom correlation. The longer monitoring time allows a higher likelihood that the patient will correlate symptoms with acid exposure and not simply by chance alone.

Combining increased sensitivity of detecting AEAE and correlation of symptoms to acid exposure may be helpful in selecting patients who will benefit from antireflux therapy. This is one weakness of the current study. We did not attempt to correlate either symptomatic severity or other objective findings of GERD (e.g., esophagitis, hiatal hernias, and barium swallow results) to the results of Bravo testing. Although this might contribute to the validation of our results, it was believed that the inhomogeneous nature of the study population (e.g., preoperative and postoperative, typical and atypical symptoms) would make these data difficult to interpret. Such a study would be best done in a prospective fashion on a designated patient population.

These data also suggest that with this new capability in measuring a longer period of esophageal acid exposure, old thresholds in determining "gastroesophageal reflux disease" will need to be revisited. It is well documented that transnasal 24-hour pH studies result in lifestyle behavior modifications that may confound the accuracy of the data collected. Therefore, using threshold values for conventional 24-hour pH monitoring and applying them to 48-hour monitoring may not be appropriate. It also has been shown in several studies that the percentage of total time the pH was less than 4 in conventional 24-hour pH and 48-hour wireless pH monitoring is significantly different for both healthy controls and patients with GERD. There is no clear consensus whether 48-hour wireless pH monitoring yields a higher or lower percentage of total time the pH was less than 4 in patients with GERD when

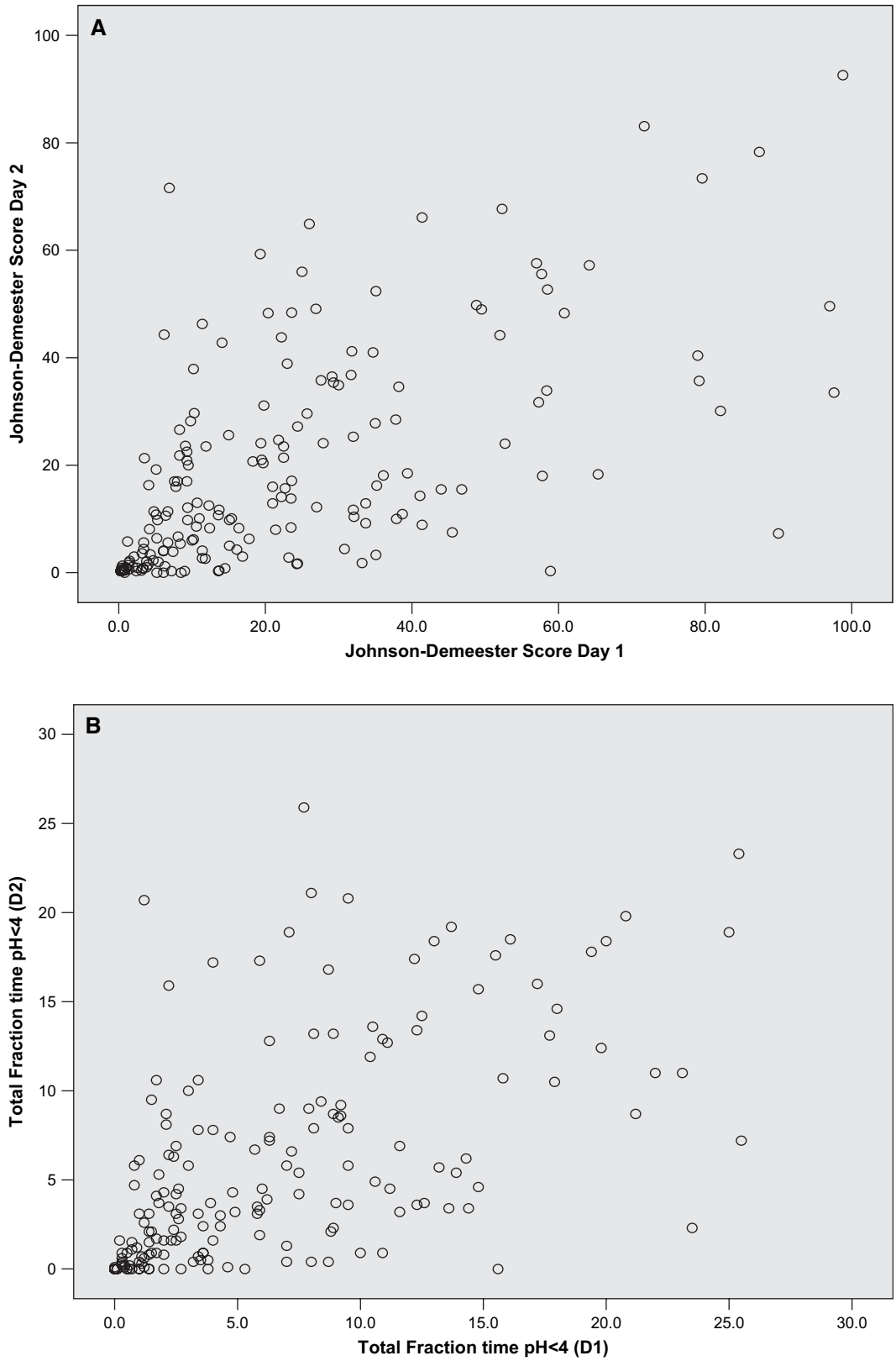

Fig. 3. (**A**) DeMeester scores for all 190 studies. Pearson's correlation coefficient with $r = 0.642$ ($P < .001$). (**B**) Percentage of total time pH was less than 4 for all 190 studies; $r = 0.600$, $P < .001$.

Table 3. Abnormal esophageal acid exposure comparison

(A) Prevalence of AEAE on Day 1 and Day 2 using different probe placement technique

	EGD (%)	Manometry (%)	*P* value
Day 1 (−), Day 2 (−)	37	42	.96
Day 1 (−), Day 2 (+)	11	9	.34
Day 1 (+), Day 2 (−)	15	16	.87
Day 1 (+), Day 2 (+)	37	33	.49

(B) Similar comparison of AEAE on Day 1 and Day 2 for patients who were off PPIs for 5 days versus 7 days. Significant differences were found at a *P* value < .05.

	5 days (%)	7 days (%)	*P* Value
Day 1 (−), Day 2 (−)	42	42	.59
Day 1 (−), Day 2 (+)	8	12	.72
Day 1 (+), Day 2 (−)	14	15	.81
Day 1 (+), Day 2 (+)	35	31	.62

EGD = esophagogastroduodenoscopy; AEAE = abnormal esophageal acid exposure; PPI = proton-pump inhibitor.

compared with conventional 24-hour pH monitoring. Pandolfino et al.[9] suggest that a threshold for 48-hour wireless pH monitoring of 5.3% be used, whereas Bruley des Varannes et al.[13] set a threshold of 2.9%. In healthy controls, Antoniazzi et al.[8] discovered that the Bravo device results yielded a higher percentage of total time the pH was less than 4 than 24-hour pH monitoring (2.6 vs. 1.5, $P = .005$), but similar overall Johnson-DeMeester scores. One hypothesis for a higher percentage of total time the pH was less than 4 in patients with a Bravo device speaks to the ability of patients to resume normal lifestyle patterns better than those who were tested with conventional 24-hour pH probes. Our study was not designed to determine the proper threshold necessary for determining AEAE. However, we did demonstrate that 48-hour monitoring will discover more patients with AEAE than 24-hour alone monitoring, regardless of whether the Johnson-DeMeester score or the percentage of total time the pH was less than 4 is used.

The use of an implantable, wireless 48-hour probe was not without its technical imperfections. Early dislodgement occurred early on as nurses and physicians were learning to implant the probe properly. Manufacturing issues early on were thought to play a role in early dislodgement and failure of some probes. Although approximately 10% of patients had insufficient data to include in the study, the majority of these cases were because of lack of patient compliance in keeping the recording unit within 5 feet of the probe as recommended by the manufacturer. However, because the probe may stay attached to the esophageal mucosa for approximately 7 days, simply replacing the recording unit may allow the procedure to be salvaged. Regardless, proper patient education and instruction are paramount in satisfactory collection of data, which needs to be reinforced by the provider.

CONCLUSION

In this study we demonstrated in a large number of patients that the wireless 48-hour esophageal pH monitoring system improves the detection of AEAE over what would have been achieved with the classic 24-hour tube-based system. This technology also has obvious advantages over conventional 24-hour pH monitoring by being much less obtrusive to patients. This advantage in comfort also suggests that the data recorded with this technology are more likely to be reflective of that occurring in normal daily activity versus the tube-based system in which patients frequently modify their behavior and likely alter their normal esophageal acid exposure. Because of the extended recording time, the Bravo device may be able to detect 22% or more patients with AEAE who would be otherwise missed in a 24-hour study alone. These findings reiterate that GERD is not always a daily event, and in a large number of patients GERD occurs only intermittently.

In determining threshold values to define AEAE, it is unclear whether old normative values are appropriate to use. More data are accumulating that the percentage of total time the pH was less than 4 may not apply to patients with a Bravo device and that a threshold over 5.3% may be too insensitive. What the optimal cutoff value should be remains unknown. Whether the Johnson-DeMeester scoring system should be used with wireless 48-hour pH data remains unclear. However, these data support the continuing use of the Johnson-DeMeester score at this time. Further investigation in determining appropriate threshold values for the Bravo probe and its usefulness for directing the treatment of GERD remains an important area of future research.

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Discussion

Dr. Marco Patti (San Francisco, CA): I want to congratulate you for a very elegant presentation and stress that this is a study from three centers in Portland and Seattle that are well known for their interest and expertise in the treatment of reflux disease. The focus of this study was on the diagnosis of reflux by using a wireless capsule, which can be implanted on the esophageal mucosa, allowing recording for 48 hours. The authors propose that this new technique has many advantages over the classic 24-hour pH monitoring, as it avoids the discomfort associated with wearing a catheter for a long time, allowing recording in more physiologic conditions and over a longer period of time. This increases the sensitivity of the test and the ability to correlate reflux episodes to reflux events. After reading the article that was kindly provided by Dr. Tseng, I have the following questions for the authors.

You had 214 studies available for analysis but you had to exclude 24, or 12.6%, because of technical reasons. Can you tell us why there was such a high failure rate?

The second question relates to the placement of the capsule, usually, as you said, 5 to 6 cm above the squamocolumnar junction. However, I think that the placement by endoscopy might be difficult in patients with Barrett's esophagus or with very large hiatal hernias, and I wonder if in these patients standard localization of the lower esophageal sphincter by manometry should be performed. In addition, I have some reservations about performing manometry through the nose, as you did in some patients, and then placing the capsule through the mouth by adding 6 cm. I think that the variation between mouth and nose is anywhere between 5 and 10 cm, depending on the size of the patient. Why not perform the manometry through the mouth?

I have two more questions. What was the gain in the symptoms index correlation for atypical and typical symptoms when the first 24 hours were compared with the 48-hour study?

Finally, different from your presentation but at the end of your article you leave us with the uncertainty about the threshold values to determine what constitutes an abnormal esophageal acid exposure as you state that the optimal cutoff value for pH less than 4 remains unknown and whether the Johnson-DeMeester scoring system should be used remains unclear. For some of us who are planning to switch to the Bravo, I think we will need a more definitive answer as we have when we use the classic 24-hour pH monitoring and study done with a catheter.

Overall, I think that this study is very important. It helps define the strengths and weaknesses of this new technique, which might have a very important place in the future for the diagnosis of reflux disease.

Dr. Tseng: Thank you, Dr. Patti, for the honor of being our discussant. Our high failure rate was in part caused by the exclusion of those patients with less than 18 hours of data in less than one of the two 24-hour periods, and we actually made that a rather rigorous definition. In fact, if you look at some of the prior studies, they used cutoffs of 14 hours. We chose to do that because we wanted to have a very rigorous and well-defined population.

I think a lot of these failures occurred early on in our experience when the devices were not quite as good; they have moved the companies from Europe

to the United States now for manufacturing reasons. Also, it is a wireless probe. So the patients can leave them at the bedside, leave them at the kitchen table and walk away, and if they are outside of the range of 5 feet, the recording mechanism stops. So that is both an advantage and a disadvantage of this system.

With regard to placement, in patients with Barrett's esophagus and especially those with long-segment Barrett's, our endoscopists use the proximal gastric folds and then measure 5 to 6 cm above that point.

Our study was not really designed, at least at this time, to correlate symptoms and indices with typical and atypical symptoms to the results of the studies, and that really will have to be done at a later date.

In regard to which scoring system to use or which threshold to use, I think at this point from the results of Dr. DeMeester's group, who have already shown that in 20 patients with the Bravo probe, the total DeMeester score, which is really a weighted score, is essentially not statistically significant from their prior study. This demonstrates, at least for the time being, that it seems appropriate to continue to use the Johnson-DeMeester score as it currently states.

Dr. Tom DeMeester (Los Angeles, CA): Dr. Tseng, you have presented an interesting and provocative study. We have just completed a similar study with the Bravo capsule placed on the basis of manometry, which raises the question that Dr. Patti raised in regard to the correct position of the Bravo capsule. We found discordance in only one patient. So placement may be the issue. I think that if patients have reflux, correct placement of the Bravo capsule is critical. In a person who does not have reflux, proper placement is less important.

The second question I have is did you control diet? The pH of food or drink will vary the result of the pH monitoring from one day to the next. Perhaps the best way to have done your study was to monitor patients for 24 hours initially, wait 2 weeks, and monitor them for 48 hours and determine how many patients had abnormal results based on a 24-hour study versus a 48-hour study. Of course, the capsule should be placed on the basis of manometry data, and diet should be controlled. This would have been better than day-to-day comparison of a 48-hour study.

I appreciate your interest in 24-hour pH manometry and your efforts to make it better.

Dr. Tseng: Thank you. To address your first question about the diet control, we actually didn't control their diets. We basically informed them to go ahead and resume their normal dietary activity as much as possible. I think a lot of these patients tend to do that just because they don't experience quite as much dysphagia and discomfort from the transnasal probe.

The second question actually has been looked at in a small number of patients. They have looked at 24-hour ambulatory pH at one time period and then brought them back 1 to 6 weeks later and did another 24-hour pH, and they did show a discordance in results, not quite as much as ours; in fact 7 of 32 patients had a difference in their diagnosis from one test compared with the other. This discordance provided background to our thoughts behind our article today.

Idiopathic Pulmonary Fibrosis: How Often Is It Really Idiopathic?

Marco G. Patti, M.D., Pietro Tedesco, M.D., Jeffrey Golden, M.D., Steven Hays, M.D., Charles Hoopes, M.D., Adam Meneghetti, M.D., Tanuja Damani, M.D., Lawrence W. Way, M.D.

The cause of idiopathic pulmonary fibrosis (IPF) is unknown. The pathology suggests that IPF results from serial lung injury. It has been suggested that gastroesophageal reflux disease (GERD) may relate to the cause or the progression of the disease. The aims of this study were to determine the prevalence of GERD, the clinical presentation of GERD, and the manometric and reflux profiles in patients with end-stage IPF. Between July 2003 and October 2004, 18 patients with IPF on the lung transplant waiting list were referred for evaluation to the Swallowing Center of the University of California San Francisco. On the basis of the results of the pH monitoring test (5 and 20 cm above the lower esophageal sphincter), the patients were divided into two groups: group A, 12 patients (66%), GERD+; group B, 6 patients (34%), GERD−. The incidence of heartburn and regurgitation was similar between GERD+ and GERD− patients; reflux was clinically silent in one third of GERD+ patients. Reflux was associated with a hypotensive lower esophageal sphincter and abnormal esophageal peristalsis, and it was present in the upright and supine position. The reflux often extended into the proximal esophagus. These results show the following: (1) Two thirds of patients with IPF had GERD; (2) symptoms could not distinguish between those with and without GERD; (3) reflux occurred in the presence of a hypotensive lower esophageal sphincter and abnormal esophageal peristalsis; and (4) reflux occurred in the upright and supine positions, and often extended into the proximal esophagus. We conclude that patients with IPF should be screened for GERD, and if GERD is present, a fundoplication should be performed before or shortly after lung transplantation. (J GASTROINTEST SURG 2005;9:1053–1058) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Interstitial lung disease, idiopathic pulmonary fibrosis, gastroesophageal reflux disease, aspiration, esophageal manometry, ambulatory pH monitoring

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease of unknown origin that is characterized clinically by dyspnea and nonproductive cough, radiologically by diffuse pulmonary infiltrates, and pathologically by varying degrees of inflammation and fibrosis.[1] Diagnosis is based on a typical history, exclusion of other known causes of interstitial lung disease, such as collagen vascular disease, and a lung biopsy showing the characteristic histopathologic picture. The disease is usually progressive and fatal, and because medical therapy is usually ineffective, lung transplantation offers the only chance for survival. Although a latent viral infection and cigarette smoking were previously thought to be the most likely causes of IPF, gastroesophageal reflux disease (GERD) is now being postulated as having a major etiologic role.[2–4]

The aim of this study was to determine the prevalence of GERD, the clinical presentation of GERD, and the manometric and reflux profiles in patients with IPF.

PATIENTS AND METHODS

Between July 2003 and October 2004, 18 patients with IPF, who were on the lung transplant list, were referred for evaluation at the Swallowing Center of

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the University of California San Francisco. There were 8 women and 10 men, whose mean age was 57 years. The average time since the initial diagnosis of IPF was 48 months.

Symptomatic Evaluation

The patients estimated the severity of their symptoms (heartburn, regurgitation, and cough) using a 5-point scale ranging from 0 (no symptom) to 4 (disabling symptom). They were also questioned about the use of acid-reducing medications (H2-blocking agents, proton pump inhibitors) and their effect on the symptoms.

Barium Swallow

The presence of a hiatal hernia was recorded.

Endoscopy

The presence and degree of esophagitis were recorded.

Esophageal Manometry

Patients were studied after an overnight fast as previously described.[5] Medications that might interfere with esophageal motor function (i.e., calcium channel blocking agents, nitrates, and metoclopramide) were discontinued at least 48 hours before the study. Position, pressure, and length of the lower esophageal sphincter (LES) were measured using the station pull-through technique. Esophageal body function was assessed by giving 10 wet swallows of 5 mL of water at 30-second intervals. The data were analyzed using a commercially available software program (Gastrosoft, Medtronics Inc., Minneapolis, Minnesota).

Ambulatory pH Monitoring

Acid-suppressing medications were discontinued 3 days (H2-blocking agents) to 14 days (proton pump inhibitors) before the study. The pH catheters were calibrated in a standard buffer solution at pH 1 and pH 7 before and after monitoring. We used pH catheters with two antimony sensors located 15 cm apart, which were passed transnasally to position the two sensors 5 and 20 cm above the upper border of the manometrically determined LES.[6] During the study, the patients consumed an unrestricted diet and took no medications that could interfere with the results. Esophageal acid exposure (percentage of time pH $<$ 4.0) in the upright and supine positions was calculated for the distal and proximal esophagus using a commercial software program (Gastrosoft, Medtronics Inc.). The exposure to refluxed acid was considered abnormal if the total time the pH was less than 4 was more than 3.5% in the distal esophagus,[7] and more than 1% in the proximal esophagus.[8] Data were incorporated into a composite score (i.e., DeMesteer score); a score greater than 14.7 was set as abnormal.[7]

Statistical Analysis

The sign test, chi-square test, and Student *t* test were used for statistical evaluation of the data. All results are expressed as mean ± standard deviation. Differences were considered significant at P less than .05.

RESULTS

On the basis of the pH monitoring results, the patients were divided into two groups: group A, GERD+, 12 patients (66%); group B, GERD−, 6 patients (34%).

There was no difference in the incidence or severity of heartburn and regurgitation in the two groups (Table 1). One third of the patients in group A experienced no symptoms suggestive of GERD. There was no difference in the symptomatic response to proton pump inhibitors.

Barium swallow showed a hiatal hernia in 75% of the patients in group A and in none of the patients in group B ($P < .05$).

Esophagitis was present in 17% of the patients in group A but in none of the patients in group B ($P < .05$).

Table 2 shows the manometric characteristics of the two groups. The LES was hypotensive (LES pressure $<$ 14 mm Hg) in 75% of patients in group A but in none of the patients in group B ($P < .05$). Abnormal peristalsis was more frequent in group A ($P < .05$).

Table 3 shows the reflux profile in the two groups. Among the patients in group A, 25% had supine reflux, 33% had upright reflux, and 42% had mixed reflux (upright and supine). Abnormal reflux was found in the proximal esophagus in 50% of patients in group A (Table 4).

Table 1. Incidence of symptoms

Symptoms	Group A	Group B	*P* value
Heartburn (% patients)	67	33	NS
Regurgitation (% patients)	33	33	NS
Cough (% patients)	84	83	NS
Response to proton pump inhibitors (% of relief)	70	60	NS

NS = not significant.

Table 2. Manometric findings

	Group A (% of points)	Group B (% of points)	*P* value
Hypotensive LES	75	0	< .05
Normal LES	17	83	< .05
Normal peristalsis	25	66	< .05
Abnormal peristalsis	75	34	< .05

LES = lower esophageal sphincter. Normal LES pressure 14 to 24 mm Hg.

DISCUSSION

These results show the following in patients with IPF: (1) The prevalence of GERD was 66%; (2) GERD was associated with a hypotensive LES and abnormal esophageal peristalsis; (3) GERD occurred in the upright and supine positions, and often extended into the proximal esophagus; and (4) symptoms did not distinguish between those with and without GERD.

Prevalence of Gastroesophageal Reflux Disease in Patients With Idiopathic Pulmonary Fibrosis

It has been suggested for years that GERD might be a cause of progressive lung damage and fibrosis. In 1971, Sladen et al.[9] proposed that aspiration of gastric contents could lead to pneumonitis and lung damage, whereas Pearson and Wilson[10] postulated a connection between hiatus hernia and diffuse pulmonary fibrosis. Later studies showed that GERD was often present in patients with chronic cough, hoarseness, and adult-onset asthma.[11–14] More recently, Tobin and colleagues[3] demonstrated that patients with IPF had an increased prevalence of abnormal esophageal acid exposure.

In the present study, GERD was detected in two thirds of our patients with end-stage IPF, and special characteristics were noted that are probably of pathophysiologic and therapeutic significance. In half of group A, reflux extended to 20 cm above the LES. Similarly, Tobin et al.[3] found reflux 15 cm above the LES in 69% of patients. High gastroesophageal reflux like this is more dangerous than reflux confined to the distal esophagus because it predisposes to microaspiration, which eventually can lead to chronic lung damage.[6,15] Supine (nocturnal) reflux was present in 67% of patients, which is particularly worrisome, because refluxed acid under these circumstances is cleared slowly, gravity cannot assist esophageal clearance, swallowing is less frequent, and saliva production is low.

Table 3. 24-hour pH monitoring

	Group A	Group B	*P* value
No. reflux episodes	286 ± 100	43 ± 27	<.05
No. episodes >5 min	10.8 ± 8.4	0.3 ± 0.8	<.05
Total % time pH < 4	20.6 ± 12	1.4 ± 1	<.05
Upright % time pH < 4	18.6 ± 11	2.2 ± 1.6	<.05
Supine % time pH < 4	20 ± 17	0.2 ± 0.4	< .05
DeMeester score	81.7 ± 42	6.7 ± 4.1	< .05

Distal channel (5 cm above lower esophageal sphincter).

Table 4. 24-hour pH monitoring

Group A	Distal reflux (5 cm above LES)	Proximal reflux (20 cm above LES)
No. reflux episodes	286 ± 100	27 ± 27
No. episodes >5 min	10.8 ± 8.4	1.1 ± 1.6
Total % time pH < 4	20.6 ± 12	2.0 ± 2.7
Upright % time < 4	18.6 ± 11	1.8 ± 2.0
Supine % time < 4	20 ± 17	2.1 ± 3.4

LES = lower esophageal sphincter.
Group A: distal and proximal reflux.

Clinical Presentation of Gastroesophageal Reflux Disease in Patients With Idiopathic Pulmonary Fibrosis

Symptoms did not distinguish between patients with IPF with and without GERD, as others have shown.[16,17] In general and despite commonly held beliefs, symptoms correlate poorly with abnormal reflux. For instance, among 822 patients referred to us with a diagnosis of GERD, manometry and pH monitoring showed that only 575 patients (70%) actually had reflux.[17] Reflux was found in 34% of patients with IPF who had none of the typical symptoms (i.e., heartburn and regurgitation) of GERD. Consequently, every patient with IPF should undergo esophageal manometry and pH monitoring, because GERD is so common, and this is the only reliable way to detect it.

Pathophysiology of Gastroesophageal Reflux Disease in Patients With Idiopathic Pulmonary Fibrosis

Patients with IPF with GERD typically had a hypotensive LES and weak esophageal peristalsis. We and others previously reported that a pan-esophageal motor disorder is often the underlying cause of upward extension of gastric contents and respiratory symptoms. Ineffective esophageal motility has particularly been singled out as an aspect of GERD associated with respiratory symptoms.[6,18] We also showed that a hiatal hernia was more common in

patients with IPF with reflux, which parallels other reports that associate a hiatal hernia, severe reflux, and respiratory symptoms.[19]

Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis: Clinical Implications

These data show a high prevalence of GERD in IPF and are highly suggestive of a cause-and-effect relationship. The implications are important. Therapy with proton pump inhibitors can block acid secretion, but gastric contents continue to reflux into the esophagus. Even though the pH is neutralized, gastric juice is still aspirated, and it still injures the lungs.[20] A fundoplication is indicated, for it is the only way to halt the cycle. For obvious reasons GERD should be diagnosed and a fundoplication should be performed as early in the course of the disease as possible.[15,21]

In patients with end-stage IPF, a fundoplication should be performed before the lung transplant if the patient's respiratory status allows. Otherwise it should be performed immediately afterward because acid reflux is probably a causative factor in the *bronchiolitis obliterans syndrome*, the most common cause of morbidity and mortality after lung transplantation.[22–24]

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Discussion

Dr. Carlos Pellegrini (Seattle, WA): Mr. Chairman, ladies and gentlemen. Dr. Pietro Tedesco has very elegantly presented to you a study of 18 patients with idiopathic pulmonary fibrosis, a relatively rare disease, in fact with a prevalence of only 13 or 15 per 100,000, yet a progressive, incapacitating disease

and a major reason for end-stage lung disease requiring transplantation.

As he told you, we initially described the high incidence of abnormal gastroesophageal reflux in patients with IPF and suggested in our first article that given the nearly 90% incidence of abnormal reflux in these patients that this was in fact the cause for IPF. Therefore, I was surprised to see that you found abnormal reflux in only 12 of 18 patients who were a selected group of patients with IPF in that they were already on the transplant list, and I would have expected that those would be the patients who were worse off.

In a more recent study that will be published soon, we describe 65 consecutive patients with IPF studied over a year and a half period, and once again, we found the incidence of reflux to be 90% in this group, with 75% having distal reflux and 66% having proximal reflux, a finding similar to yours.

So I wonder, as my first question, if you would like to give us your thoughts about what do you attribute the finding of a lower incidence of reflux in the patients you studied, a population who we would have expected had more rather than less reflux? One possible explanation, because we have a control group of patients who have interstitial lung disease as opposed to IPF, a disease that is not that easy to separate, is that perhaps this represents some patients with interstitial lung disease. I am wondering what is the diagnostic method you used? Perhaps you can tell us, did you use biopsies on these patients, did you have the clinical and radiologic characteristics of it, and did you have pulmonary function tests on them and so forth?

My second question relates to the treatment recommendations, as you expressed on the last slide. You said that an antireflux procedure should be performed before or just after pulmonary transplant. I do not believe that you have shown data to support that conclusion. I know it is difficult to control acid reflux with proton pump inhibitors (PPIs), and in fact in a group of 19 patients in whom we performed 24-hour pH monitoring before and after triple-dose treatment with PPIs, we found that we could only control reflux in 12 of the 19 patients. On the other hand, operations in these patients are not without substantial risk.

We have experienced one death, for example, in our group of patients with IPF who underwent Nissen fundoplication, and we have experienced certainly much more frequent recurrence than in patients without IPF. Thus, I am not sure that without a major prospective study we can recommend liberal use of antireflux procedures in these individuals as the group at Duke, and now yours, is recommending.

On the other hand, we have seen that pulmonary function and symptoms of IPF improve or remain stable, remarkably stable over a period longer than 5 years, which is usually the time in which most of these patients die, when control of reflux is achieved with very high doses of PPIs or with a combination of surgery and PPIs.

Could you then share with us your experience with regard to the medical and surgical treatment of this condition? In how many patients were you able to control reflux with medical means alone? What dosage of medication are you using? More important, have you noticed any preservation of pulmonary function or any improvement in pulmonary function in that group of patients?

I appreciate the opportunity to review the excellent article before the meeting and I thank you for the opportunity to do so.

Dr. Tedesco: I want to thank Dr. Pellegrini for reviewing our article and giving us his constructive feedback. I will answer his questions in the order they were asked:

All of our patients had end-stage disease with idiopathic pulmonary fibrosis and were on the lung transplant list. All of them had been carefully studied, and the diagnosis of idiopathic pulmonary fibrosis was reached after exclusion of all other known causes of interstitial lung disease.

I really don't have an explanation for the lower prevalence of GERD in our study, 66% instead of 94%. In our study, the probe was always placed after manometric localization of the lower esophageal sphincter. In contrast, in other studies, it was done without manometry, therefore exposing to the risk of false-positive results.

Our protocol calls for every patient with IPF to have 24-hour pH monitoring, and if the study is negative, it will be repeated after the lung transplantation, because there is evidence as suggested by the group at Duke University that reflux may develop after the transplant. If the study is positive, and patients are considered high risk for surgery before the transplant, they are treated with high doses of PPIs. If the patient is in satisfactory conditions, a laparoscopic Nissen fundoplication is performed before the lung transplant, because the goal of a Nissen fundoplication is to stop episodes of microaspiration and damage to the transplanted lung. To date, we have operated on four patients only, with an average hospital stay of 48 hours and no complications. We agree with Dr. Pelligrini about the need to evaluate the results objectively by pH monitoring.

Dr. Steven DeMeester (Los Angeles, CA): Very interesting topic and nicely presented. I wondered how many of your patients were positive at the proximal probe only and negative at the distal probe, and did those get counted as patients who were reflux positive? Second, what were your criteria for being positive at the proximal probe?

How many patients had absolutely no symptoms but yet had documented reflux in this group of patients? As a corollary, respiratory symptoms are known to exacerbate reflux disease. Did you explore the duration of reflux symptoms? How many patients had reflux symptoms that predated their pulmonary disease by a long period of time versus how many got their symptoms as their pulmonary disease progressed?

Dr. Tedesco: In response to Dr. DeMeester's questions, we found that some patients had few episodes of reflux distally but more proximally. We do not know the meaning of this finding, and we have not counted these patients as positive. We chose the 1% threshold as defined by the work of Dr. Donald Castell and by studies in volunteers in our own center.

Reflux was clinically silent in one third of GERD-positive patients. The median duration of reflux symptoms was 48 months.

Quality-of-Life After Total Pancreatectomy: Is It Really That Bad on Long-term Follow-up?

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While selected pancreatic diseases may be best treated by total pancreatectomy (TP), the anticipated sequelae of pancreatic insufficiency make TP an undesirable alternative. Our aim was to determine if patients undergoing TP have a worse quality of life (QoL) than age- and gender-matched controls and poor long-term glycemic control. Ninety-nine patients undergoing TP from 1985 through 2002 were identified. The 34 survivors with no recurrent malignancy were surveyed with the Short Form-36 (SF-36), the Audit of Diabetes Dependent QoL (ADD QoL), the European Organization for Research and Treatment in Cancer Pancreas 26 (EORTC PAN 26), and our institutional questionnaire. Operative morbidity and mortality were 32% and 5%, respectively. Three late postoperative deaths (3%) were attributed to hypoglycemia. Of the 34 surviving patients, 27 (79%) agreed to participate at a mean of 7.5 years postoperatively. Seven patients had required 12 hospitalizations for poor glycemic control. Per the SF-36, two domains (role physical and general health) were decreased compared with an age- and gender-matched national population ($P < .05$). The ADD QoL demonstrated an overall decrease in QoL related specifically to the diabetes mellitus ($P < .01$), but comparison with insulin-dependent diabetics from other causes showed no significant difference in QoL. The EORTC PAN 26 instrument also showed measurable effects on QoL. Total pancreatectomy can be performed safely. QoL after TP is decreased compared with age- and gender-matched controls but not with diabetes from other causes; however, the changes are not overwhelming. TP should remain a viable option but in selected patients. (J GASTROINTEST SURG 2005;9:1059–1067) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Total pancreatectomy, pancreatic insufficiency, diabetes mellitus, quality of life, intraductal papillary mucinous neoplasm

The goal of surgical management of pancreatic pathology is often directed at excision of the diseased parenchyma, thus preserving functional pancreatic parenchyma to maximize pancreatic exocrine and endocrine function. Total pancreatectomy (TP) reached its zenith of popularity in the 1960s as surgeons desired to decrease the perioperative morbidity associated with pancreatic anastomoses while also striving to improve the oncologic outcomes of the surgical treatment of pancreatic ductal cancer, fueled by the now erroneous theory of multicentricity.[1,2] Over the past two decades, TP has been relegated largely to extraordinary situations in which the pancreas is involved diffusely with symptomatic or potentially malignant disease, is unsuitable for an anastomosis, or is extirpated during salvage pancreatectomy. Currently, the increased recognition of intraductal papillary mucinous neoplasms (IPMNs) has prompted some surgeons to advocate TP, believing the entire duct to be at risk for neoplasia.[3]

The relative trepidation with which a surgeon approaches TP is not unwarranted. Historically, TP was associated with morbidity and mortality rates greater than those for partial pancreatectomy.[4] Difficulty arose with management of postoperative brittle diabetes and dangerous episodes of hypoglycemia.

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As survival in these patients was limited due to malignancy, little long-term follow-up has been available. To our knowledge, no substantive, long-term evaluation of the impact of the apancreatic state on glycemic control and quality of life (QoL) has been published in the literature.

QoL is an important adjunct in measuring the burden of chronic disease, as seen in the eyes of the apancreatic patient. The impact of postoperative diabetes on the perception of well-being and its influence on daily life is best assessed over the long-term by using validated QoL instruments. This study analyzes the long-term effect of TP on glycemic control and QoL.

METHODS

This study was approved by our institutional review board on July 22, 2003. Ninety-nine consecutive patients who had undergone TP at the Mayo Clinic from 1985 through 2002 were reviewed retrospectively. Clinical and pathologic factors were analyzed, and substantive postoperative morbidity, as well as 30-day or "in-hospital" mortality, was evaluated. Patients who were still alive at the time of this study received the Short Form-36 (SF-36), the Audit of Diabetes Dependent QoL (ADD QoL), the European Organization for Research and Treatment in Cancer Pancreas 26 (EORTC PAN 26), and our institutional, nonvalidated survey developed to assess glycemic control. Our institutional survey evaluated mean glycosylated hemoglobin, amount of weight loss or gain, daily dosages of insulin and pancreatic enzyme replacements, and number of hospitalizations for poor glycemic control.

The SF-36 is a generic health status survey in which participants are scored against age- and gender-matched controls, thereby allowing comparisons of disease burden against the norm.[5] The SF-36, which evaluates eight separate domains of QoL from the patient's aspect, is divided into four domains of physical well-being and four domains of mental well-being. These eight domains can be grouped into two separate composite scores of overall physical health and mental health. The instrument is standardized to a score of 50 for the age- and gender-matched normal controls.

The ADD QoL and EORTC-PAN 26 are disease-specific instruments. The ADD QoL focuses on the impact of diabetes on a patient's perception of well-being allowing for comparison to a cohort of diabetics not secondary to TP.[6] This validated instrument analyzes 18 separate domains related to the effects of diabetes mellitus and summarizes the overall response by a mean (or median) weighted score. The instrument is standardized to a score of zero when the diabetes mellitus has no impact on the domain evaluated; this instrument uses a standardized response from insulin-dependent diabetics (n = 795), not a normal population of nondiabetic controls.

The EORTC-PAN 26 was developed to measure health status and disease burden among pancreatic cancer patients specific to the treatment of their disease; no "normal" controls are available for analysis of the responses to the EORTC-PAN 26.[7] This validated instrument was developed as a survey specific for pancreatic cancer and surveys 10 categories of well-being from the patient's perspective. Although not designed specifically for patients after TP and without recurrent disease, we believe that a pancreas-specific instrument would be enlightening. Three of the domains evaluated by the questionnaire involve symptoms of metastatic disease (hepatic symptoms, cachexia, and ascites); responses to these were deleted.

Means and ranges or medians were used as data summaries for continuous measures depending on normalcy of distribution, and counts and percentages were used for discrete variables. The Kaplan-Meier survival method was used to describe patient survival subsequent to hospital discharge (n = 95).[8] Both χ^2 and Fisher's exact test were used as appropriate to evaluate univariate associations of the risk factors.[9,10] The Wilcoxon rank-sum test was used to evaluate domain scales from the two validated established survey instruments (SF-36 and ADD QoL).[11] Values from the EORTC PAN 26 were evaluated empirically.

RESULTS

Ninety-nine (67 malignant, 32 benign) consecutive patients undergoing TP between 1985 and 2002 at the Mayo Clinic, Rochester, Minnesota, were identified; 80 underwent primary resections and 19 underwent completion pancreatectomies. Fifty-three men and 46 women had a mean age of 61 years (range, 26–80 years). Diabetes mellitus was present preoperatively in 32 patients (32%). Operative and histopathologic characteristics are outlined in Table 1. The overall morbidity rate was 32%. The most common complications after TP were delayed gastric emptying (8%), intra-abdominal abscess requiring drainage (6%), and wound infection or line sepsis (4% and 3%, respectively). Two patients required reoperation: one for drainage of a rectus sheath hematoma and one for a small

Table 1. Clinical and Pathologic Characteristics of Patients Undergoing Total Pancreatectomy (TP) (1985–2002)

	All Patients (n = 99)	Died (n = 65)	Survived* (n = 34 [34%])
Male (n)	53	40	13
Female (n)	46	25	21
Primary TP (n)	80	57	23
Completion TP (n)	19	8	11
Preoperative diabetes mellitus (n)	32	18	14
Pathologic diagnosis (n)			
Ductal adenocarcinoma	33	31	2
IPMN with CIS or invasive adenocarcinoma	17	10	7
Periampullary adenocarcinoma	5	3	2
Islet cell neoplasm	6	5	1
Other malignancy	6	5	1
Cystic neoplasm of pancreas	3	2	1
IPMN	9	0	9
Chronic pancreatitis	20	9	11

IPMN = intraductal papillary mucinous neoplasms; CIS = carcinoma in situ.
*As of last follow-up.

bowel obstruction. Overall hospital or 30-day operative mortality was 5%: three patients died secondary to postoperative hemorrhage and ensuing coagulopathy, and one patient each died on postoperative day 44 and 45 secondary to hepatic failure and to a myocardial infarction, respectively.

Long-term survival was estimated for the patients not considered as a hospital or 30-day operative mortality. Among the patients with malignant pathology, the median and 5-year survivals were 24 months and 34% (95% confidence interval [CI], 24%–48%), respectively. Those with benign pathology had a median and 5-year survival of 15.3 years and 84% (95% CI, 71%–100%) (Fig. 1). Three patients died of complications secondary to severe hypoglycemia between 7 and 9 years postoperatively.

Twenty-seven of the 34 (79%) survivors elected to participate in this study. These patients completed surveys at a mean of 7.5 years. Although 19 patients (70%) reported weight loss (mean, 12 kg; range, 2–31 kg), 7 (28%) reported weight gain (mean, 11 kg; range, 2–36 kg). Weight loss or gain did not differ between those with benign or malignant pathologies ($P = .81$). A mean of 14 tablets/capsules (range, 0–36) of pancreatic enzyme supplements were taken per patient per day. The mean insulin dose was 32 units/day (range, 2–66). The mean glycosylated hemoglobin (Hb_{A1c}) concentration (normal <7.0%) was 7.4% (range, 5.0%–11.3%). The cumulative follow-up was 205 patient-years. Of the 27 patients, 7 patients were hospitalized 12 times for either hypoglycemia (n = 7) or hyperglycemia (n = 5), yielding a risk of hospitalization secondary to poor glycemic control of 0.06 per patient year and 0.2 per patient.

QoL Survery Instruments

The SF-36 survey demonstrated a decrease in two of the eight domains (role physical and general health) compared with age- and gender-matched national normative population (i.e., a mean score of 50) ($P < .03$) (Fig. 2). The overall composite score for physical health was also lower in the surveyed patients ($P = .01$). A subgroup analysis comparing patients after TP with and without diabetes mellitus preoperatively showed no domain to be different for these two groups ($P > .05$, two-sided t test assuming unequal variances; data not shown). There were no significant differences in the two composite scores.

The ADD QoL (standardized to a value of zero, which means diabetes has no effect on perception of QoL) revealed a negative impact secondary to the obligate diabetes induced by TP with a mean weighted score of −1.9 (standard deviation, 1.6; $P < .01$). Analysis of the 18 individual domains revealed a negative impact of diabetes in every area of life ($P < .01$ each) except physical appearance ($P = .08$) and societal reaction ($P = .06$) (Fig. 3). When compared with diabetics not secondary to TP, there was a significant decrease in only one domain: ease of traveling ($P = .01$). The perceived impact of diabetes on QoL after TP was not significantly different from the standard normal population of insulin-dependent diabetics; the mean weighted scores were −2.0 versus −1.9. In a subgroup analysis comparing those patients after TP in our cohort with and without preoperative diabetes, the mean weighted scores were not different (−1.7 versus −2.2; $P < .46$).

Although the EORTC PAN-26 has no established normative data, the qualitative impact of disease, the impact of treatment, and effect on sexuality were evaluated by the instrument (Fig. 4). Patients noted substantial dissatisfaction with symptoms of pain, body image, operative side effects, and their expectations of health care. Unfortunately, the ability to correlate these results with other controls is not available.

DISCUSSION

TP was once the preferred treatment for pancreatic ductal adenocarcinoma (secondary to the

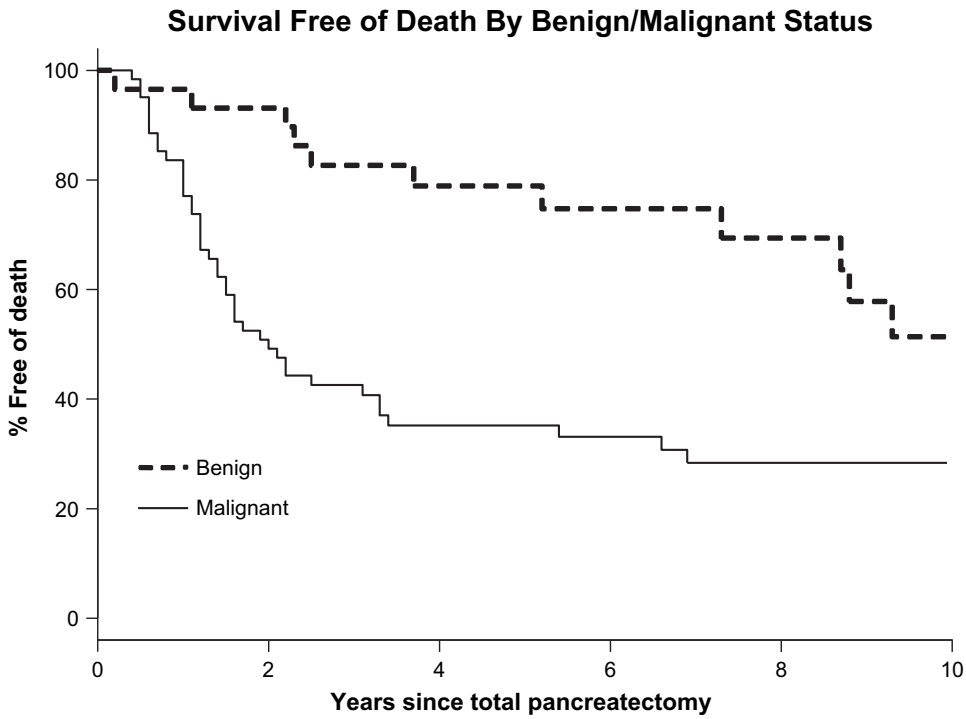

Fig. 1. Survival after total pancreatectomy in patients with and without malignant pancreatic etiology; Kaplan-Meier curves.

presumption of multicentric disease) in an attempt to improve oncologic outcomes and avoid anastomotic complications of a partial pancreatectomy.[1,2] Subsequent series failed to find an advantage of TP over subtotal resection in either safety or survival.[4] Moreover, detailed histopathologic studies have shown ductal cancer of the pancreas not to be a multicentric disease.[12] Additionally, the endocrine derangement attendant to the apancreatic state often created a brittle diabetic state.[4] In addition to these concerns of glycemic control, the added negative effects of the lack of pancreatic exocrine secretions has further discouraged the use of TP as a common treatment for diffuse disease of the pancreas, and especially so in patients with chronic pancreatitis. Thus, many surgeons have avoided the use of TP in patients who are not deemed reliable in their self-care (e.g., alcoholic chronic pancreatitis) or those who are medically unsophisticated in their insight into the health aspects of the apancreatic state. Unfortunately, no long-term evaluation of glycemic control or QoL has been investigated satisfactorily.

The operative morbidity rate of TP in this series (32%) is similar to that published for partial pancreatectomy (22%–41%) and for TP (32%–64%) reported from other institutions during the same time period.[13-23] The mortality rate (5%) is within the range of published mortality rates for partial pancreatectomy (0%–4%) and TP (0%–14%).[15,17–19,21–24] The median and 5-year survival for TP patients with malignant pathology was similar to that of patients undergoing a pancreatoduodenectomy for ductal adenocarcinoma (24 months and 35% versus 13–17 months and 17%–24%, respectively).[23–26] Included in the malignancy category are IPMN with invasive adenocarcinoma (n = 7), islet cell neoplasms (n = 6), and periampullary neoplasms (n = 5), which explains the slightly improved results in this series over previous reports of survival in patients with only ductal cancer of the pancreas. Subgroup analysis of survival by pathologic diagnosis or completeness of resection was not performed due to the small number of patients in each group. Five-year survival after TP for benign disease is similar to that published previously for partial pancreatectomy in the surgical management of chronic pancreatitis (80%–88%).[18,22]

The glycemic control of this series appears to be improved compared with earlier studies. The mean reported Hb_{A1c} level of 7.4% (range, 5.0%–11.3%) reflects glycemic control close to that advocated for decreasing the risk of diabetic microvascular and renal complications and is lower than previously published TP series (9.4%–10.3%).[17,18,27] Likewise, the risk of hospitalization secondary to hypoglycemic complications is similar to hospitalization rates

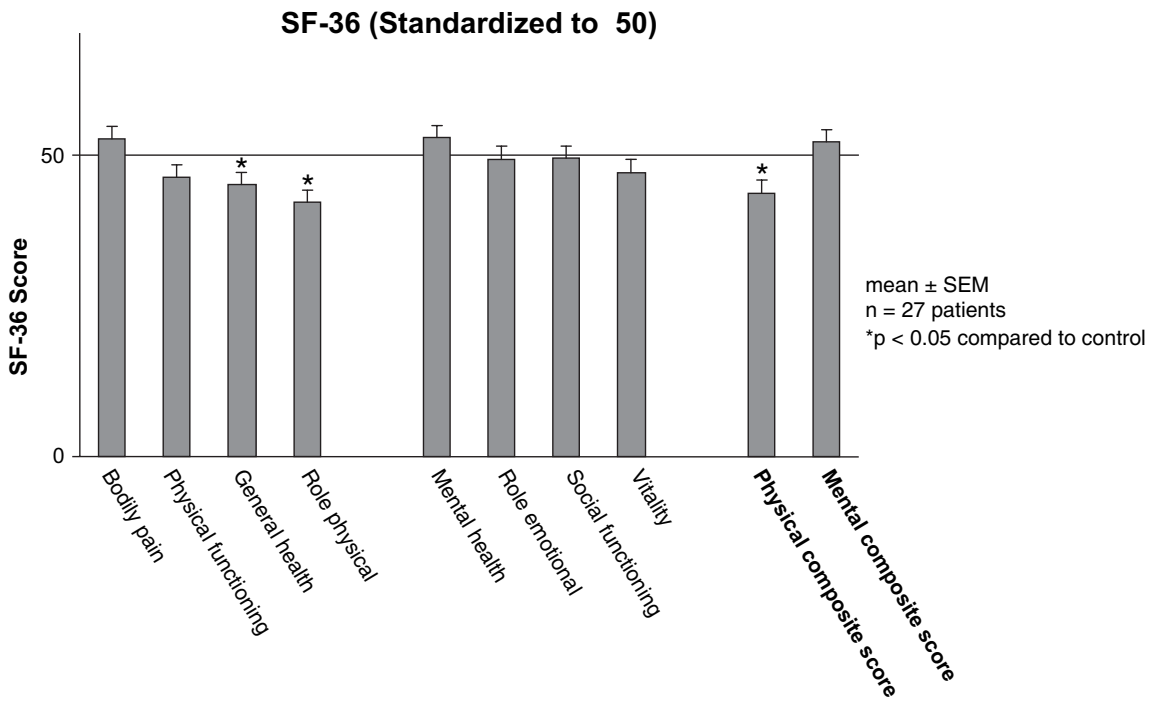

Fig. 2. Results of SF-36 in patients after total pancreatectomy standardized to the score of 50 for normal age- and gender-matched controls. The physical composite and mental composite scores are the summary values of physical well-being and mental well-being.

among patients with insulin-dependent diabetes (from other causes) reported elsewhere.[28–33] The relatively low Hb_{A1c} is likely, in part, due to the loss of glucagon counterregulation; however, apancreatic hyperglycemia or ketosis is still possible as seen in this series and other publications.[29] Although adequate glycemic control was achieved among the surviving respondents, there was a 3% overall risk of late death secondary to hypoglycemia in the entire cohort, and the limitations of this retrospective review prevent inference of the glycemic control in those not alive or unavailable for follow-up.

The results of the SF-36 demonstrate a significant negative impact of TP on long-term health status in two of the eight domains (role physical and general health) compared with age- and gender-matched controls. The scores of four domains (physical functioning, vitality, social functioning, and role emotional), while reduced, did not reach statistical significance. As the SF-36 measures the impact of disease on health, it is not a true QoL measure. QoL is, instead, inferred from the ability of the patient to perform activities of daily living. These results, however, suggest that TP patients do experience a significant decrease in their perception of the quality of their health and their ability to live and work.

Similar responses were seen with the ADD QoL, which was developed specifically to evaluate the effects of diabetes mellitus on patients' views of their QoL. The ADD QoL measures a patient's perception of the impact diabetes has had on their enjoyment of life and their ability to work, socialize, and plan for the future. It also allows the respondent to rank the importance of each domain in their life. Similar to insulin-dependent diabetes mellitus from other causes, the apancreatic diabetic patient expressed an almost universal negative impact of diabetes on their QoL; no category examined by the survey was enhanced by diabetes. When compared with a control population of insulin-dependent diabetics from all causes, the apancreatic diabetic had a significant decrease in only one domain: ease of traveling ($P < .01$); however, the average weighted score was not different. These results demonstrate that the negative impact of diabetes on QoL after TP is not, however, remarkably different from that of "normal" insulin-dependent diabetics.

The EORTC PAN 26 was designed to examine QoL changes specific to the patient with pancreatic cancer. While there is no normative data with which to compare our results,[34] it allows additional insight into the long-term effects of TP on QoL. While patients experienced negative symptoms after TP, the

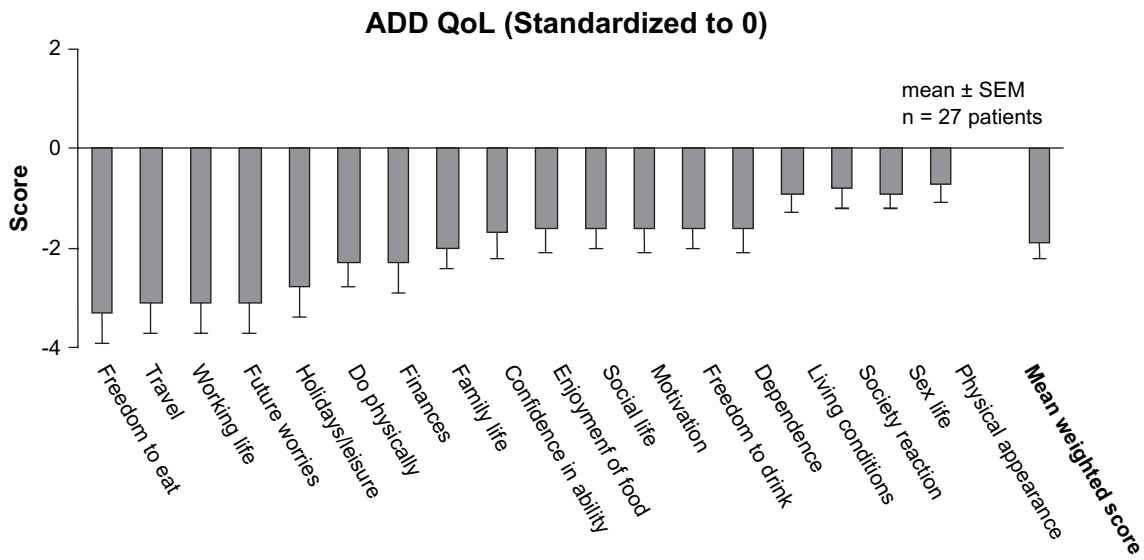

Fig. 3. Results of ADD Quality of Life (QoL) after total pancreatectomy; the standardized score of zero means that diabetes mellitus has no effect on QoL.

significance compared with others with pancreatic disease remains unknown.

The morbidity and mortality presented in this series affirm the relative safety of TP. Additionally, the average risk of hospitalization secondary to hypoglycemia and maintenance of near appropriate Hb_{A1c} in the long-term survivors suggests that apancreatic diabetes is tenable in selected patients.

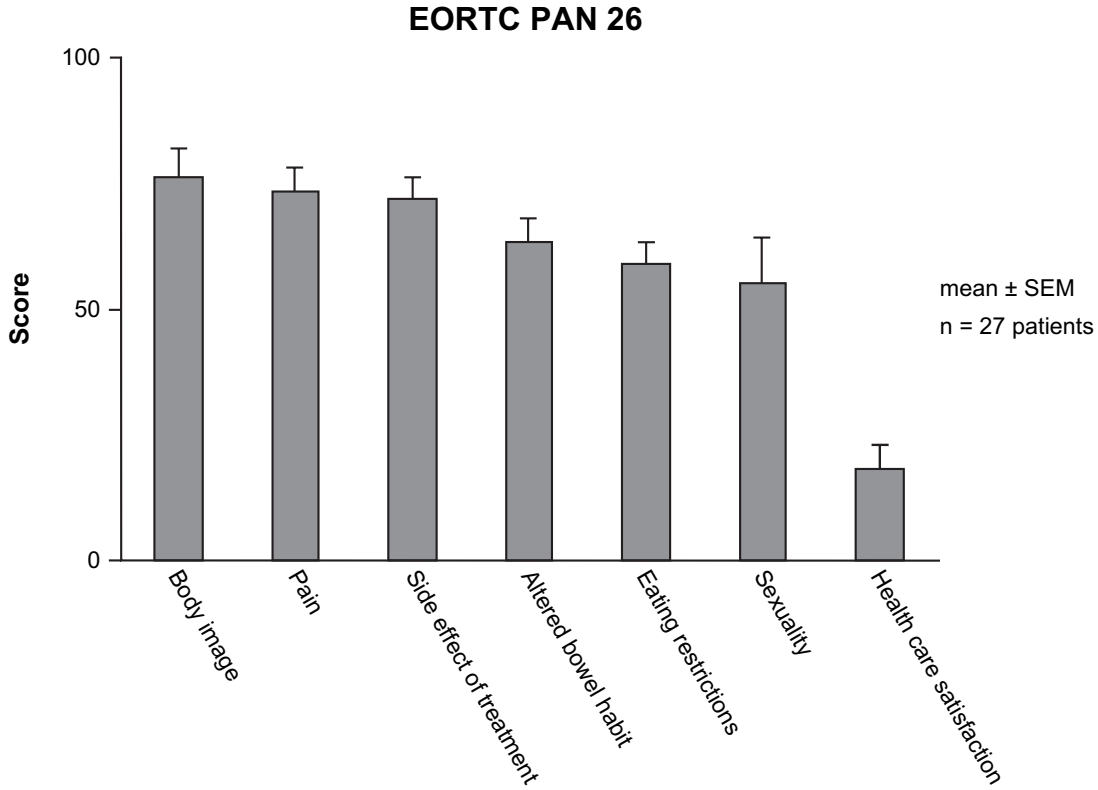

Fig. 4. Results of EORTC PAN 26 after total pancreatectomy. Note: no normative, control data are available for comparison, and we deleted the categories of hepatic symptoms, cachexia, and ascites since all patients were free of disease. Also, for health care satisfaction, a greater score means greater satisfaction.

There remains, however, a late risk of death secondary to hypoglycemia; indeed, three patients died of hypoglycemic attacks. The results of the SF-36 and ADD QoL demonstrate a significant decrease in patients' perception of their health status and a significant decrease in QoL secondary to postoperative diabetes. The QoL compared with diabetics from other causes, however, is not remarkably different.

Our study suggests that when evaluated by validated instruments in long-term survivors without evidence of recurrent malignancy, TP does substantially affect health status and QoL as evaluated by the patient. Control of the obligate diabetes mellitus can be difficult; indeed 3 of 99 patients died of hypoglycemia, and the specific effects of diabetes impacts QoL. Nevertheless, the effects of TP are not overwhelming in the majority of survivors. Thus, in carefully selected patients with motivation, adequate medical support, and appropriate education and insight about the effects of the apancreatic state, TP should remain a viable option for certain pancreatic disorders.

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Discussion

Dr. Charles Yeo (Baltimore, MD): I rise to congratulate Dr. Billings and his other teammates at the Mayo Clinic-Rochester for this wonderful presentation. I understand it is his first national presentation. So congratulations, Brian, and cheers also for winning the resident award.

This is really quite a large number of patients about whom the Mayo Clinic are reporting today. In comparison, at the 2004 Pancreas Club last year in New Orleans, the well-known group from Italy led by Dr. Pedrazzoli reported on 32 patients who had undergone total pancreatectomy over a 10-year period and talked about quality of life in 21. So to my knowledge, this paper today gives us the largest group of single-institution survivors of total pancreatectomy who are assessed for quality of life.

Some data to keep in your memory that were in the manuscript but Brian did not have a chance to present today: patients in this study took a mean of 14 tablets or capsules of pancreatic enzymes and used a mean insulin dose of 32 units per day. In the Italian study, remarkably, they used 31 units of insulin per day. So very similar. Further, in the Mayo study, with a cumulative follow-up of over 200 patient years, you noted there were 12 hospitalizations, yielding a risk of hospitalization at about 0.06 hospitalization per patient per year. Low but not trivial.

The quality of life survey results were very well done using those three tools, they were well interpreted, and they are really not surprising. I think what these data tell us is that in the powers of evolution or intelligent design, whatever we believe in, someone did very well in creating a pancreas that impacts endocrine/exocrine function very well. We as surgeons need to be careful, conservative, and reflective when we consider total pancreatectomy. Yes, our patients can take pancreatic enzymes; yes, they can monitor their blood sugars carefully, but total pancreatectomy clearly has an adverse impact on quality of life.

Three questions for the authors. First, you made the point to state that total pancreatectomy remains a viable option, but in selected patients. Let's get down to the nitty-gritty here. So what patients should have a total pancreatectomy?

Second, the analyses of quality of life data are always nebulous. They are a little bit soft any time this is done. You received 27 forms back from 27 patients. Did the patients write in the margins as they sometimes do? Do you get the sense that they are thankful to be alive without a pancreas, taking enzymes and using insulin, or do you get the sense that they feel that a disservice has been done to them?

And last, with the recent significant advances in euglycemic control, and I am referring to the newer insulin preparations, the synthetic analog of human amylin (pramlintide acetate), and the inexpensive and more friendly glucometers and all, predict the future for us a bit, Brian. Where will we be in 10 to 20 years vis-á-vis total pancreatectomy for premalignant or malignant processes? What will the future generation of these patients be like? How will they be managed? Can we anticipate that their quality of life will be better?

I thank the group from the Mayo Clinic for this wonderful work, and the SSAT for the privilege of asking some questions.

Dr. Billings: Thank you, Dr. Yeo. To answer the first question as to which patients for whom we consider total pancreatectomy to be advisable. I think the answer comes in two parts; first, goal-directed excision should remain the norm for pancreatic pathology. I believe the pathology of the duct and the gland should determine the extent of resection.

Second, I think that patient selection is key as is any procedure that sets up an iatrogenic chronic disease process, much like transplantation. I think the doctor-patient relationship in this area is paramount. The patient must understand exactly what impact apancreatic diabetes will have on their Quality of Life and Health Status. Additionally, they must have the insight to deal with the apancreatic diabetes well. If those can be satisfied, then I think the patient would have an adequate quality of life.

As for the future of total pancreatectomy with newer insulin preparations, I think it is difficult to know. With our ability to more closely monitor diabetes and regulate the effect of exogenous insulin, with long- and short-acting insulin preparations, I think survival has improved. When you look back to the studies that were performed in the 1960s, the mortality rate due to glycemic complications was much higher. But it still requires quite a bit of

time and effort to monitor their blood sugar and their diet. I think the exocrine dysfunction, which we never addressed in this study, also requires close monitoring. So while apancreatic diabetes will likely always have a significant impact on quality of life, due to the intensive effort to control their disease, I believe their health status will improve.

Dr. Michael Zenilman (Brooklyn, NY): This is a very nice study. I did not know there were 99 patients in the United States who underwent total pancreatectomy. As you mentioned in the beginning of your talk, it has really gone out of favor, especially in the era of techniques that spare pancreatic parenchyma. Nonetheless, this is a very, very nice study.

My question is: did you consider matching your quality of life surveys to controls at Mayo? For example, could you match to pancreatic cancer patients who did not undergo total pancreatectomy, and to pancreatitis patients who underwent procedures that preserved parenchyma? For the diabetics, could you match them to diabetics who are taken care of by your medical colleagues?

Dr. Billings: We would like to take a look at long-term survivors after pancreaticoduodenectomy and compare them with SF-36 and the ADD QOL. Additionally, hopefully when more results are available with the EORTC PAN 26, we will be able to compare those patients as well.

Dr. Fabrizio Michelassi (New York, NY): Brian, first of all, congratulations on a very clear presentation and nice paper. I was wondering whether the answers to the quality of life questionnaires were different if the patients were or were not diabetic preoperatively?

Dr. Billings: One third of these patients were diabetic preoperatively. When we did subgroup analysis looking at preop diabetes specifically, there was no difference in the quality of life between the two groups after total pancreatectomy.

Dr. Teri Brentnall (Seattle, WA): Wonderful, really wonderful assessment of these patients. I wanted to ask you a couple of questions about hypoglycemia. You had three patients who died of hypoglycemia. Did they have more than one event of hypoglycemia?

Dr. Billings: This follow-up was performed by telephone surveys and speaking with family survivors. I know one patient had repeated episodes of hypoglycemia. He had alcoholic pancreatitis and had multiple episodes, I believe four, before he died of aspiration pneumonia.

Dr. Brentnall: And did your hypoglycemic patients have symptoms of hypoglycemia or could they not detect that they were becoming hypoglycemic?

Dr. Billings: All three of the patients who died secondary to hypoglycemia had alcohol pancreatitis, which I believe interfered with their ability to maintain glycemic control. We never inquired about neuroglycopenic symptoms.

Dr. Brentnall: So you are thinking that perhaps they continued to be alcoholics after their pancreas was removed?

Dr. Billings: Correct.

Dr. Brentnall: You might want to note that in your manuscript, because that correlation there about people dying of hypoglycemia and maybe having the symptoms obscured by their drinking issues is a very interesting observation, and people who have recurrent hypoglycemia might be candidates for pancreas transplantation. If someone is an active alcoholic, that probably wouldn't be advisable, but you have got the largest study to date, so this is really very important information.

Dr. Billings: Thank you.

5-Fluorouracil and Gemcitabine Potentiate the Efficacy of Oncolytic Herpes Viral Gene Therapy in the Treatment of Pancreatic Cancer

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Oncolytic herpes viruses are attenuated, replication-competent viruses that selectively infect, replicate within, and lyse cancer cells and are highly efficacious in the treatment of a wide variety of experimental cancers. The current study seeks to define the pharmacologic interactions between chemotherapeutic drugs and the oncolytic herpes viral strain NV1066 in the treatment of pancreatic cancer cell lines. The human pancreatic cancer cell lines Hs 700T, PANC-1, and MIA PaCa-2 were treated in vitro with NV1066 at multiplicities of infection (MOI; ratio of the number of viral particles per tumor cell) ranging from 0.01 to 1.0 with or without 5-fluorouracil (5-FU) or gemcitabine. Synergistic efficacy was determined by the isobologram and combination-index methods of Chou and Talalay. Viral replication was measured using a standard plaque assay. Six days after combination therapy, 76% of Hs 700T cells were killed compared with 43% with NV1066 infection alone (MOI = 0.1) or 0% with 5-FU alone (2 μmol/L) ($P < .01$). Isobologram and combination-index analyses confirmed a strongly synergistic pharmacologic interaction between the agents at all viral and drug combinations tested (LD_5 to LD_{95}) in the three cell lines. Dose reductions up to 6- and 78-fold may be achieved with combination therapy for NV1066 and 5-FU, respectively, without compromising cell kill. 5-FU increased viral replication up to 19-fold compared with cells treated with virus alone. Similar results were observed by combining gemcitabine and NV1066. We have demonstrated that 5-FU and gemcitabine potentiate oncolytic herpes viral replication and cytotoxicity across a range of clinically achievable doses in the treatment of human pancreatic cancer cell lines. The potential clinical implications of this synergistic interaction include improvements in efficacy, treatment-associated toxicity, tolerability of therapeutic regimens, and quality of life. These data provide the cellular basis for the clinical investigation of combined oncolytic herpes virus therapy and chemotherapy in the treatment of pancreatic cancer. (J GASTROINTEST SURG 2005;9:1068–1079) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Herpes simplex virus, NV1066, synergism, viral oncolysis

Pancreatic cancer is an aggressive malignancy that is the fourth leading cause of cancer-related deaths for both men and women in the United States.[1,2] In 2005, adenocarcinoma of the exocrine pancreas will account for an estimated 31,860 new cases and 31,270 deaths.[1] Despite the recent advances in anticancer drugs, surgical resection remains the only potentially curative option for patients with pancreatic cancer. Only 10–15% of patients, however, are resectable at the time of diagnosis.[3] Moreover, survival after presumed curative resection remains poor with median survivals ranging from 17 to 21 months.[3–8]

For patients with distant disease or locally advanced disease precluding resection, the prognosis

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is worse with median survivals ranging from 3 to 10 months.[2] A multitude of therapeutic regimens using chemotherapeutic agents and radiation have been investigated. While 5-fluorouracil (5-FU)- and gemcitabine-based regimens have demonstrated the greatest antitumor effect, only negligible improvements in survival have been realized. It is clear that novel therapeutic options are needed for the treatment of pancreatic cancer.

Oncolytic herpes viruses are attenuated, replication-competent herpes simplex type 1 viruses (HSVs) that selectively infect, replicate within, and lyse cancer cells. These viruses have been shown to be highly efficacious in the treatment of a wide variety of human and animal cancers.[9–18] Recent studies in our laboratory and others suggest that the efficacy of oncolytic HSV is enhanced when administered in combination with ionizing radiation or chemotherapeutic agents.[12,19–22] This observation is not universal, however, depending on both the chemotherapeutic agent or viral strain used and the individual cancer. Combined modality therapeutic regimens are attractive as they aim to exploit a synergistic interaction between two agents to maximize efficacy and reduce treatment-associated toxicity and the development of drug resistance. As we envision combining oncolytic HSV with current chemotherapeutic regimens for the initiation of human clinical trials, this study sought to investigate whether 5-FU or gemcitabine potentiates efficacy of oncolytic HSV in the treatment of pancreatic cancer.

MATERIALS AND METHODS

Cells

The human pancreatic cancer cell lines Hs 700T, PANC-1, and MIA PaCa-2 were obtained from the American Type Culture Collection (Rockville, MD) and grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with high glucose, 1.5 g/L sodium bicarbonate, 100 U/ml penicillin, 100 mg/ml streptomycin, and 10% fetal calf serum. Vero cells (American Type Culture Collection, Rockville, MD) were grown in minimum essential medium supplemented with 100 U/ml penicillin, 100 mg/ml streptomycin, and 10% fetal calf serum. Cells were maintained in a 5% CO_2 humidified incubator at 37°C.

Virus

NV1066 is an attenuated, replication-competent oncolytic HSV whose construction has been previously described.[23,24] Briefly, NV1066 is derived from the wild-type HSV-1 virus (F strain) and is rendered safe via deletions in the viral replicative and virulence genes *ICP0*, *ICP4*, and $\gamma_1 34.5$. NV1066 is a derivative of the oncolytic HSV strain NV1020, which has already been tested in human phase I clinical trials demonstrating a favorable safety profile.[25] Viral stocks were propagated on Vero cells and titered by standard plaque assay.[17]

Cytotoxicity Assay

Cytotoxicity assays were performed by plating 2×10^4 cells into 24-well flat-bottom assay plates (Becton Dickinson, Franklin Lakes, NJ) in 1 ml of media. After overnight incubation at 37°C, cells were treated with either media alone (control), 1–4 μmol/L 5-FU (American Pharmaceutical Partners, Schaumburg, IL), 0.5–2 nmol/L gemcitabine (Eli Lilly and Company, Indianapolis, IN), or NV1066 at multiplicities of infection (MOI, the ratio of viral plaque-forming units [PFU] to tumor cell) ranging from 0.01 to 1.0. Combination therapy experiments were performed by first exposing cells to either 5-FU or gemcitabine for 6 hours. After exposure, the media containing the chemotherapeutic agent was removed, cells were washed with phosphate-buffered saline (PBS), and fresh medium was added. Cells were then infected with NV1066 diluted in 100 μl media and incubated at 37°C. Daily after infection, media was removed and cells were lysed with 1.35% Triton-X solution to release intracellular lactate dehydrogenase (LDH). LDH was then quantified with the Cytotox 96 nonradioactive cytotoxicity assay (Promega, Madison, WI) that measures conversion of a tetrazolium salt into a red formazan product. Absorbance was measured at 450 nm with a microplate reader (EL321e; Bio-Tek Instruments, Winooski, VT). Results are expressed as the surviving percentage of cells as determined by the measured absorbance of each sample relative to control, untreated cells. All samples were tested and experiments were replicated, in triplicate.

Quantitative Analysis of Synergy

The isobologram and combination-index (CI) methods, derived from the median-effect principle of Chou and Talalay, were used to define the pharmacologic interaction between the chemotherapeutic drugs and NV1066.[26] Details of these equations and of the software used to perform the computerized analyses have been described previously.[26–30] Briefly, by taking into account the potency of the individual drugs, the potency of the combination of the drugs, and the shapes of their dose-effect curves, these methods enable the precise analysis of the pharmacologic interaction of two-drug combinations

by comparing observed drug effects with predicted additive drug effects.

Data obtained from the cytotoxicity experiments were used to perform these analyses. The isobologram method is a graphical representation of the pharmacologic interaction and is formed by selecting a desired fractional cell kill (Fa) and plotting the individual drug and viral doses required to generate that Fa on their respective x- and y-axes. A straight line is then drawn to connect the points. The observed dose combination of the two agents that achieved that particular Fa is then plotted on the isobologram. Combination data points that fall on the line represent an additive drug-drug interaction, whereas data points that fall below or above the line represent synergism or antagonism, respectively.

The CI method is a mathematical and quantitative representation of a two-drug pharmacologic interaction. Using data from the cytotoxicity experiments and computerized software, CI values are generated over a range of Fa levels from 0.05 to 0.95 (5–95% cell kill). CI of 1 indicates an additive effect between two agents, whereas a value of $CI < 1$ or $CI > 1$ indicates synergism or antagonism, respectively. More clinically pertinent, data generated from the CI method can be used to quantify the dose-reduction index (DRI) for the combination of two drugs. DRI represents the fold-decrease of each individual agent attainable if the two drugs are used in combination as opposed to alone to achieve a particular Fa.

Viral Replication Assay

Standard plaque assays were performed to quantify viral proliferation within pancreatic cancer cells. Cells (2×10^4) were plated in 12-well flat-bottom assay plates in 2 ml of media. After overnight incubation at 37°C, cells were treated with NV1066 alone (MOI = 0.01) or in combination with 5-FU (1–5 μmol/L) or gemcitabine (1–5 nmol/L). Supernatants and cells were collected from culture wells 6 days following treatment. Samples were subjected to three freeze-thaw lysis cycles to release intracellular viral particles. Serial dilutions of supernatants and cell lysates were cultured on confluent layers of Vero cells and viral titers were determined by counting viral plaques 72 hours later. All samples were tested, and experiments were replicated, in triplicate.

Real-Time Reverse Transcriptase Polymerase Chain Reaction Quantification of GADD34 Expression

Cells (3×10^5) were plated in six-well plates with 2 ml of media, incubated overnight, and treated with 5-FU (10 μmol/L) or vehicle alone (control). Six hours following exposure, medium was removed, cells were washed with PBS, and fresh medium was added. Cells were harvested 12, 24, 36, and 60 hours after exposure and total RNA was isolated using an RNeasy Mini Kit (Qiagen Inc, Valencia, CA). SYBR green–based real-time quantitative reverse transcriptase polymerase chain reaction (RT-PCR) was performed using an ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The following primers were used: GADD34 forward (5′-GGAGGAAGAGAATCAAGCCA-3′), GADD34 reverse (5′-TGGGGTCGGAGCCT GAAGAT-3′), 18S forward (5′-GTAACCCGTT GAACCCCATT-3′), and 18S reverse (5′-CCATC CAATCGGTAGTAGCG-3′). Co-amplification of the 18S ribosomal RNA housekeeping gene was used to normalize the amount of total RNA present. Thermal cycling conditions for amplification of GADD34 were as follows: 95°C for 9 minutes and 30 seconds; 40 cycles of 94°C for 30 seconds, 55.6°C for 30 seconds, 72°C for 30 seconds, and 78°C for 30 seconds.

Statistical Analysis

All data are expressed as mean ± SEM. Two-tailed Student's *t* test was used to determine significance between treatment groups.

RESULTS

Cytotoxicity of NV1066 in the Treatment of Hs 700T Human Pancreatic Cancer Cells

To examine the oncolytic efficacy of NV1066, dose-dependent cytotoxicity experiments were performed. NV1066 demonstrates dose-dependent cytotoxicity against the Hs 700T human pancreatic cancer cell line (Fig. 1). Cell kill progressively increases for the duration of the experiment at all doses tested. Seven days following infection at an MOI of 1.0, 90 ± 0.3% of cells were killed ($P < .01$). Even at 10- and 100-fold lower MOIs of 0.1 and 0.01, 84 ± 1% and 63 ± 3% of cells were killed 7 days following infection, respectively ($P < .01$).

Cytotoxicity of Combination NV1066 and 5-Fluorouracil or Gemcitabine

To examine the cytotoxic effect of combining chemotherapeutic agents and NV1066, Hs 700T cells were treated with either 5-FU or gemcitabine alone, NV1066 alone, or a combination of a 5-FU or gemcitabine and NV1066. Treatment of Hs 700T cells with 2 μmol/L 5-FU alone or NV1066 at an MOI of 0.1 alone resulted in 0 ± 1% and

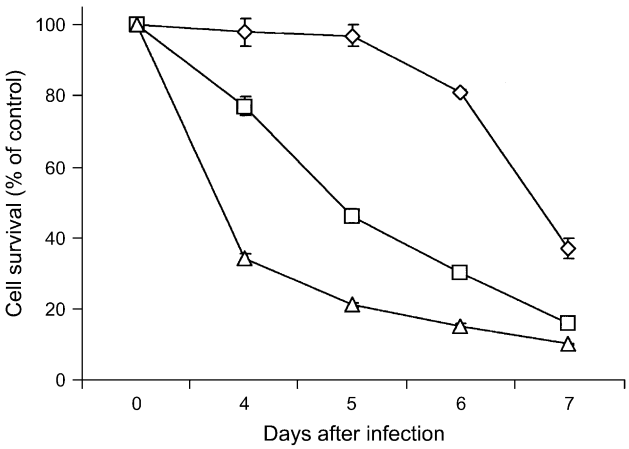

Fig. 1. NV1066 demonstrates dose-dependent cytotoxicity against the Hs 700T human pancreatic cancer cell line. Monolayer cell cultures of Hs 700T were infected with NV1066 at multiplicities of infection (MOIs) of 0.01 (*diamond*), 0.1 (*square*), and 1.0 (*triangle*). Lactate dehydrogenase cytotoxicity assays were used to measure cell kill for 7 days following infection (last 4 days are shown). Mean cell survival is presented as a percentage compared with uninfected cells (±SEM). MOI represents the ratio of the number of viral particles to the number of tumor cells.

43 ± 3% cell kill, respectively, 6 days following treatment (Fig. 2, *A*). The expected cytotoxicity of combining treatments assuming an additive pharmacologic interaction was calculated and plotted (Fig. 2, *A*, dotted line). Observed cytotoxicity with combination 2 μmol/L 5-FU and NV1066 at an MOI of 0.1 demonstrated 76 ± 4% cell kill 6 days after treatment and is significantly greater than predicted cell kill ($P < .01$).

Similar results were obtained combining gemcitabine and NV1066. Six days following treatment of Hs 700T cells with 1 nmol/L gemcitabine alone or NV1066 at an MOI of 0.1 alone, 3 ± 3% and 45 ± 5% of cells were killed, respectively (Fig. 2, *B*). Observed cytotoxicity with combination gemcitabine and NV1066 at the same doses demonstrated 71 ± 3% cell kill and is significantly greater than predicted cell kill ($P < .01$). Synergism was observed over a range of clinically achievable doses of both 5-FU (Fig. 3, *A–C*) and gemcitabine (Fig. 3, *D–F*). Synergism was also observed in the treatment of PANC-1 and MIA-PaCa-2 human pancreatic cancer cell lines (data not shown).

Quantitative Analysis of Synergy

The isobologram and CI methods developed by Chou and Talalay were used to confirm and quantify the synergism observed between the chemotherapeutic drugs and NV1066. Isobolograms were

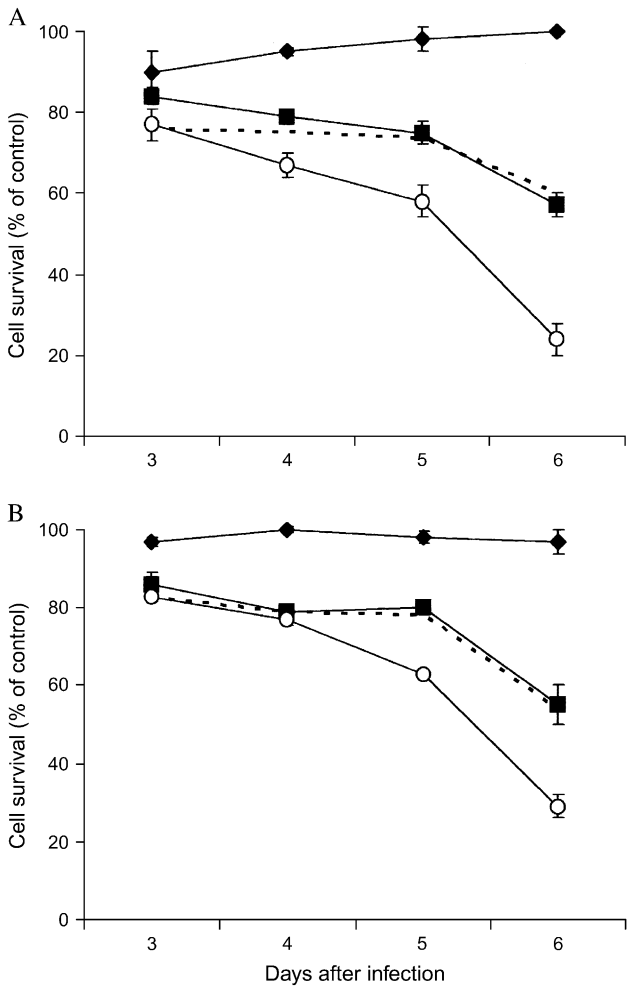

Fig. 2. Combination chemotherapy and oncolytic viral therapy demonstrate synergistic efficacy in the treatment of a human pancreatic cancer cell line. Monolayer cell cultures of Hs 700T cells were treated with 2 μmol/L 5-fluorouracil (**A**, *diamond*), 1 nmol/L gemcitabine (**B**, *diamond*), NV1066 at an MOI of 0.1 (*square*), or a combination of the chemotherapeutic agent with NV1066 (*open circle*). Lactate dehydrogenase cytotoxicity assays were used to measure cell kill on days 3, 4, 5, and 6. Expected additive cell kill was calculated and is plotted (*dotted line*). Mean cell survival is presented as a percentage compared with uninfected cells (±SEM). Multiplicities of infection (MOI) represents the ratio of the number of viral particles to the number of tumor cells.

constructed for Fa values ranging from 0.5 to 0.95 (5–95% cell kill). Experimental combination therapy data points plot well below the expected additive line at each Fa value for both combinations indicating strong synergism across a broad range of doses and agents. Representative isobolograms are shown in Figure 4.

CI values for the interaction between 5-FU and NV1066 (0.25–0.47) and gemcitabine and NV1066 (0.10–0.53) are <1 over the entire range of Fa values

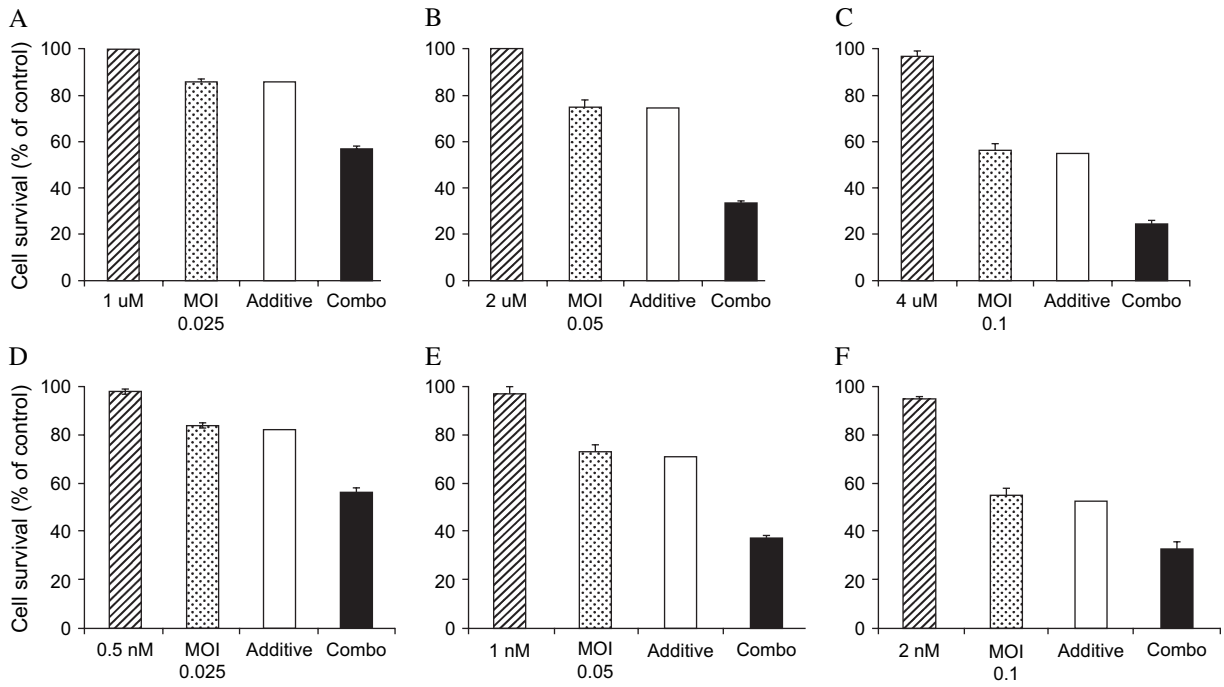

Fig. 3. Combination chemotherapy and oncolytic viral therapy demonstrate synergistic efficacy in the treatment of a human pancreatic cancer cell line over a range of chemotherapeutic and viral doses. Hs 700T cells were treated with a range of doses of 5-fluorouracil alone (**A–C**, *hatched bar*), gemcitabine alone (**D–F**, *hatched bar*), NV1066 alone (*dotted bar*), or a combination of the agents (*solid bar*). Expected additive cell kill was calculated and is plotted (*open bar*). Lactate dehydrogenase cytotoxicity assays were used to measure cell kill 6 days following treatment. Mean cell survival is presented as a percentage compared to uninfected cells (±SEM). Multiplicities of infection (MOI) represents the ratio of the number of viral particles to the number of tumor cells.

tested (0.05–0.95), indicating strong synergism (Table 1). Using these data, the DRI was then calculated for each Fa value. For combination 5-FU and NV1066, compared with either drug alone, up to 78-fold and 6-fold dose reductions can be achieved, respectively, without compromising cell kill (Table 2). For combination gemcitabine and NV1066, up to 207-fold and 10-fold dose reductions can be achieved, respectively, without compromising cell kill (Table 3). These mathematical methods therefore demonstrate a strong synergistic interaction between each chemotherapeutic drug and NV1066 over a wide range of therapeutic doses and cytotoxic effect levels.

Viral Replication Assay

Viral progeny production in Hs 700T cells was quantified in the absence or presence of 5-FU or gemcitabine using standard plaque assays (Fig. 5). Six days following infection of Hs 700T cells with NV1066 alone at an MOI of 0.01 (200 PFU), 5.6×10^4 PFU were produced. Addition of 5-FU or gemcitabine resulted in a dose-dependent increase in viral progeny production. Combination treatment with 1 μmol/L, 2.5 μmol/L, or 5 μmol/L 5-FU resulted in the production of 1.5×10^5 PFU, 1.1×10^6 PFU, and 8×10^5 PFU, respectively, 6 days following infection (Fig. 5, *A*). This represents a 750- to 5500-fold amplification of the initial infecting viral dose (200 PFU) and a 3- to 19-fold increase in viral titer production compared with cells treated with virus alone ($P < .05$). Combination therapy with gemcitabine resulted in a 2800- to 8000-fold amplification of the initial infecting viral dose representing a 10- to 30-fold increase in viral progeny compared with infection with NV1066 alone ($P < .01$) (Fig. 5, *B*).

Real-Time Reverse Transcriptase Polymerase Chain Reaction Quantification of GADD34 Expression

Real-time RT-PCR was used to assess genetic expression of the cellular stress response gene GADD34 following treatment of pancreatic cell lines with 5-FU. Six-hour exposure of Hs 700T cells to 5-FU resulted in a 2.3-fold upregulation of GADD34 mRNA expression 24 hours following treatment ($p < .01$) (Fig. 6).

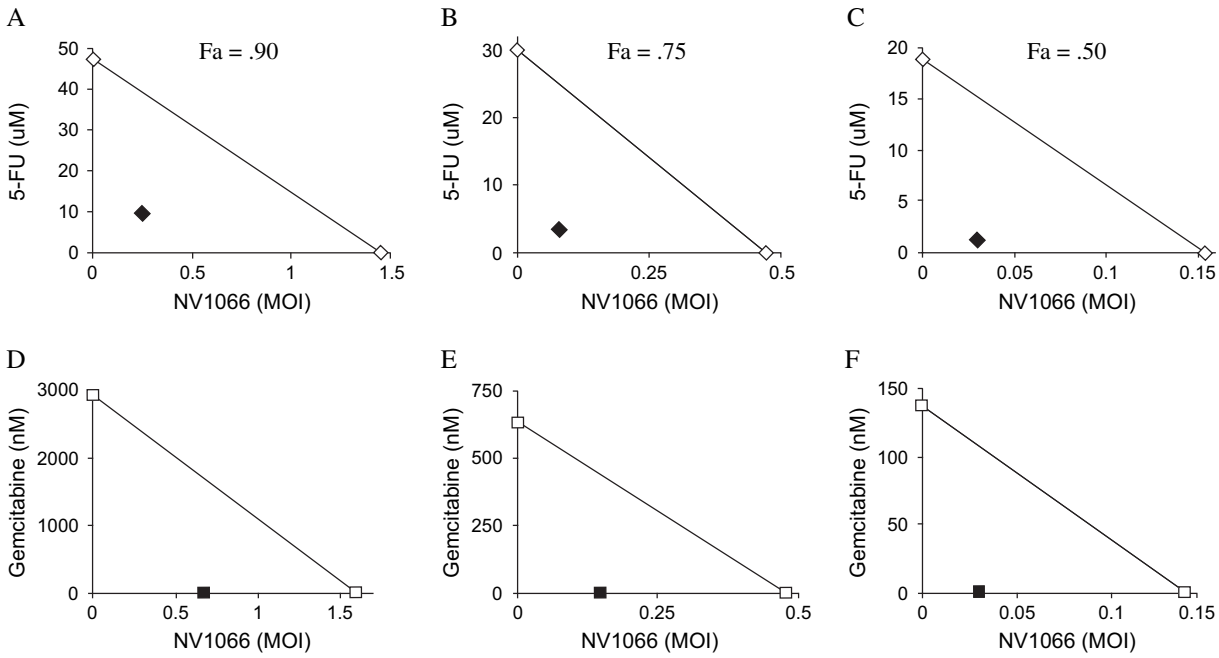

Fig. 4. Isobolograms demonstrate synergism between NV1066 and 5-FU (A–C) and NV1066 and gemcitabine (**D–F**). The individual doses of NV1066 and 5-FU observed to achieve 90% cell kill (Fa = 0.90, **A**), 75% cell kill (Fa = 0.75, **B**), and 50% cell kill (Fa = 0.50, **C**) are plotted on the x- and y-axes, respectively (open diamonds). The individual doses of NV1066 and gemcitabine needed to achieve 90% cell kill (Fa = 0.90, **D**), 75% cell kill (Fa = 0.75, **E**), and 50% cell kill (Fa = 0.50, **F**) are plotted on the x- and y-axes, respectively (*open squares*). The *solid line connecting these points* represents drug combination doses required to achieve the desired cell kill (Fa) if the pharmacologic interaction between the two agents is additive. Observed drug combination doses are plotted (NV1066 and 5-FU = *closed diamonds*; NV1066 and gemcitabine = *closed squares*) and fall well below the additive line, indicating strong synergism for both combinations over a range of doses and cytotoxic effect levels. Fa = fraction cell kill; 5-FU = 5-fluorouracil.

DISCUSSION

Novel therapies are desperately needed for the treatment of pancreatic cancer. Current chemoradiation-based therapeutic regimens are largely limited in both efficacy and toxicity. Oncolytic herpes viruses are attenuated, replication-competent viruses that selectively infect, replicate within, and lyse cancer cells and are highly efficacious in the treatment of a wide variety of experimental therapies. We have previously shown that oncolytic herpes viruses are effective as a single-agent in the treatment of an experimental model of pancreatic cancer.[14] We now use the isobologram and CI methods of Chou and Talalay to define the pharmacologic interactions between 5-FU, gemcitabine and the oncolytic HSV strain NV1066 and demonstrate a synergistic enhancement in cytotoxicity in the treatment of a human pancreatic cancer cell line.[26] Synergism was observed across a range of clinically achievable doses of two of the most effective and widely used chemotherapeutic agents in the treatment of this disease. Furthermore, synergism was observed in the treatment of all three cell lines tested although representative data from one cell line is shown.

A fundamental advantage of oncolytic viral therapy compared to standard cancer treatment modalities, is the *in vivo* amplification of the administered viral dose. Following completion of the viral life cycle in a cancer cell, cellular lysis results in the release of many new infectious viral particles which can then infect additional viable cancer cells. We demonstrate that the production of viral progeny is significantly enhanced in the presence of either 5-FU or gemcitabine. Our data also suggest that this potentiation of viral replication is responsible for the synergism observed. The differential improvement in cell kill in the combination therapy arms of the experiments does not appear to be an initial cytotoxic effect. Rather, it becomes evident five to six days following treatment after several viral life cycles have been completed and after the differential increase in viral progeny production is evident by plaque assay. This

Table 1. Combination Index (CI) Values Determined for Pharmacologic Interaction Between NV1066 and 5-Fluorouracil and NV1066 and Gemcitabine Over a Broad Range of Cytotoxic Effect Levels*

Fractional Cell Kill	CI Value (NV1066 and 5-FU)	CI Value (NV1066 and Gemcitabine)
0.05	0.25	0.10
0.10	0.24	0.13
0.20	0.24	0.16
0.30	0.25	0.18
0.40	0.25	0.21
0.50	0.26	0.23
0.60	0.27	0.26
0.70	0.28	0.29
0.80	0.31	0.34
0.90	0.38	0.43
0.95	0.47	0.53

*Interpretation of CI values in quantifying two-drug pharmacologic interactions: CI 0.90–1.10 = nearly additive; CI 0.85–0.90 = slight synergism; CI 0.70–0.85 = moderate synergism; CI 0.30–0.70 = synergism; CI 0.10–0.30 = strong synergism; CI <0.10 = very strong synergism.

amplification is limited only to the extent that viable cancer cells are present to support viral replication.

Several molecular mechanisms have been proposed to explain the potentiation of viral replication by chemotherapy and radiation therapy.[11,12,19–22,31,32] These mechanisms describe viral exploitation of the host cellular stress response following exposure to chemotherapeutic agents or ionizing radiation. Previous work in our laboratory has demonstrated that upregulation of host cellular ribonucleotide reductase (RR) following exposure of cancer cells to ionization radiation enhances viral replication and cell kill in the treatment of a colorectal cancer cell line.[21] RR reduces ribonucleotides to deoxyribonucleotides and is responsible for the production of the substrates of DNA synthesis. These studies were performed using the second-generation oncolytic herpes simplex type-1 viral strain G207, which has an insertional inactivation of the large subunit of the viral ribonucleotide reductase gene and is therefore dependent on host cell RR for viral replication. Upregulation of host cell RR following DNA damage has therefore been proposed to complement the viral genomic deletion enhancing viral replication.

In comparison to G207, NV1066 is not deficient for viral RR and is therefore not dependent on host cell RR for viral replication. More recent work from our laboratory has shown that upregulation of the host cellular stress response gene GADD34 (Growth Arrest and DNA Damage Protein 34) mediates a synergistic cytotoxic effect following exposure of gastric cancer cells to mitomycin C.[22] GADD34 is homologous to the viral replicative gene $\gamma_1$34.5—both copies of which are deleted in NV1066 for attenuation. Upregulation of GADD34 following exposure to the chemotherapeutic agent therefore complements this viral genomic deletion and enhances viral replication. We similarly demonstrate upregulation of GADD34 following exposure of Hs 700T cells to 5-FU.

The clinical implications of this synergism are evident and are not limited to enhanced efficacy. The DRI, the most relevant clinical parameter derived from the Chou and Talalay analysis, reveals the potential for significant dose reductions without compromising cell kill. Dose reductions minimize treatment-associated toxicity, thereby improving the tolerability of therapeutic regimens and quality of life.

The use of these agents alone or in combination with systemic chemotherapy can be conceivably used in several clinical settings. The retroperitoneal resection margin is the site of local failure in up to 50% of cases following pancreaticoduodenectomy.[2] Oncolytic HSV could be administered intraoperatively

Table 2. Doses of 5-Fluorouracil (5-FU) and NV1066 Needed to Kill Various Fractions (Fa) of Hs 700T Cells and Dose Reductions (-Fold) Achievable When Agents Are Used in Combination*

Fractional Cell Kill (Fa)	5-FU Alone (uM)	NV1066 Alone (MOI)	5-FU Dose Reduction Index	NV1066 Dose Reduction Index
0.05	5.3	0.007	78	4
0.1	7.6	0.016	52	5
0.15	9.2	0.026	41	5
0.2	10.6	0.037	34	5
0.25	12	0.05	29	5
0.3	13.3	0.064	25	5
0.35	14.6	0.081	22	5
0.4	16	0.101	20	5
0.45	17.4	0.125	18	5
0.5	19	0.153	16	5
0.55	20.6	0.188	14	5
0.6	22.5	0.232	13	5
0.65	24.6	0.289	11	5
0.7	27	0.367	10	5
0.75	30	0.472	9	6
0.8	33.9	0.634	8	6
0.85	39.2	0.905	6	6
0.9	47.6	1.454	5	6
0.95	65.1	3.128	3	6

*Dose-reduction index is the achievable dose reduction (-fold) for each single agent when used in combination to attain the same cell kill.

Table 3. Doses of Gemcitabine and NV1066 Needed to Kill Various Fractions (Fa) of Hs 700T Cells and Dose Reductions (-fold) Achievable When Agents Are Used in Combination*

Fractional Cell Kill (Fa)	Gemcitabine Alone (nM)	NV1066 Alone (MOI)	Gemcitabine Dose-Reduction Index	NV1066 Dose-Reduction Index
0.05	2.3	0.006	208	10
0.1	6.5	0.013	209	8
0.15	12.3	0.021	209	7
0.2	20	0.031	210	7
0.25	29.9	0.043	211	6
0.3	42.4	0.057	211	6
0.35	58.2	0.073	211	5
0.4	78.3	0.092	212	5
0.45	104.1	0.115	212	5
0.5	137.6	0.143	212	4
0.55	181.8	0.178	213	4
0.6	241.7	0.223	213	4
0.65	325.3	0.282	213	4
0.7	446.7	0.363	214	4
0.75	633.5	0.478	214	3
0.8	944.9	0.655	215	3
0.85	1533.3	0.959	215	3
0.9	2916.6	1.59	216	2
0.95	8239.5	3.61	217	2

*Dose-reduction index is the achievable dose reduction (-fold) for each single agent when used in combination to attain the same cell kill.

into the tumor bed following resection for clearance of microscopic residual disease and sterilization of this difficult margin. Locally advanced primary disease precluding resection could be approached with percutaneous or endoscopically administered virus in combination with neoadjuvant systemic chemotherapy in an attempt to downstage disease and permit subsequent curative resection. Additionally, common sites of recurrent metastatic disease include the peritoneal cavity and liver, which could be treated with regional intraperitoneal or intrahepatic arterial perfusion, respectively.

The toxicity of these agents has also been extensively investigated in both animal models and humans. Oncolytic herpes viruses are highly specific for infection of cancer cells, sparing normal cells. The safety of these oncolytic viruses has been tested in preclinical toxicology studies in *Aotus* monkeys, which are extremely sensitive to wild-type herpes viral infections. These monkeys demonstrated no toxicity when administered attenuated virus.[33,34] Viral dissemination following administration has been extensively investigated in our laboratory using both quantitative PCR detection of the viral gene *ICP0* and radiolabeled herpes virus. These studies repetitively demonstrate no viral proliferation in noncancerous tissues. Finally, the safety of use of several oncolytic HSV strains has been demonstrated in humans with the recent completion of several phase I clinical trials.[25]

CONCLUSION

We demonstrated that 5-FU and gemcitabine potentiate oncolytic herpes viral replication and

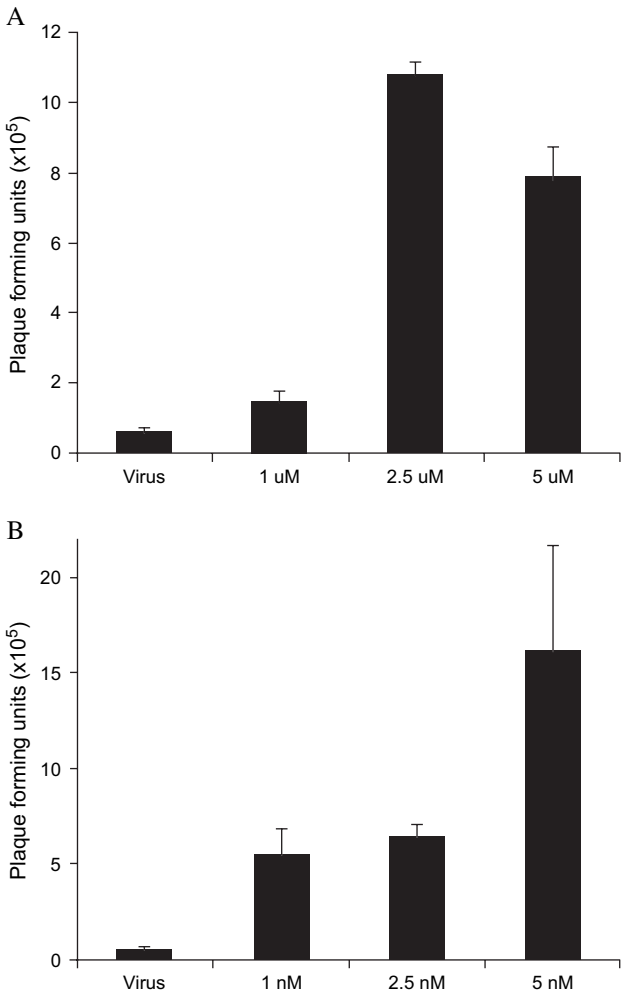

Fig. 5. Combination of chemotherapy and oncolytic viral therapy demonstrates enhanced viral replication in Hs 700T pancreatic cancer cells. Monolayer cell cultures of Hs 700T cells were treated with NV1066 at an multiplicity of infection (MOI) of 0.01 (200 plaque-forming units [PFU]) either alone or in combination with a range of doses of 5-fluorouracil (1–5 μmol/L) (**A**) or gemcitabine (1–5 nmol/L) (**B**). Viral progeny were quantified 6 days following infection using a standard plaque assay. Mean PFU for triplicate samples are plotted (±SEM). MOI represents the ratio of the number of viral particles to the number of tumor cells.

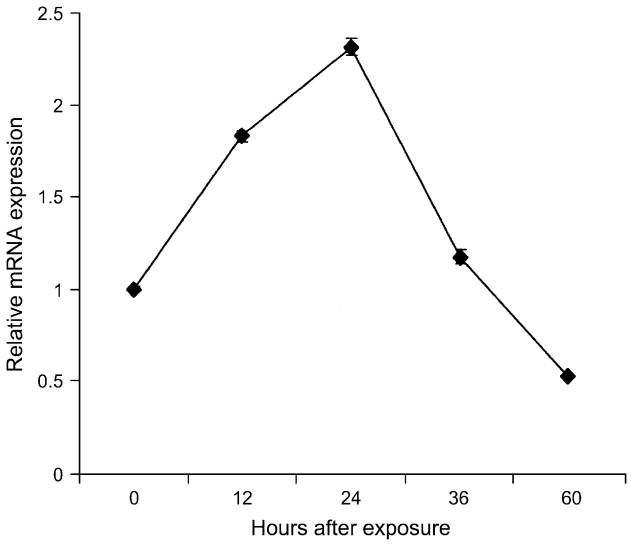

Fig. 6. GADD34 is upregulated in Hs 700T cells following treatment with 5-fluorouracil (5-FU). Monolayer cultures of Hs 700T cells were exposed to 5-FU (10 μmol/L) or vehicle alone (control) for 6 hours. Cells were harvested, and RNA was isolated 12, 24, 36, and 60 hours following exposure. Real-time reverse transcriptase polymerase chain reaction was used to quantify GADD34 mRNA expression. Data are normalized to both 18S ribosomal RNA and to control, untreated, cells. Mean relative GADD34 mRNA expression of triplicate samples is plotted (±SEM).

cytotoxicity across a range of clinically achievable doses in the treatment of human pancreatic cancer cell lines. The clinical implications of this synergistic interaction are paramount and include improvements in efficacy, treatment-associated toxicity, tolerability of therapeutic regimens, and quality of life. This data also corroborate prior studies suggesting a synergistic interaction between chemotherapy and oncolytic viral therapy and support the commencement of clinical trials incorporating oncolytic herpes viruses into investigative therapeutic regimens in the treatment of pancreatic cancer.

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Discussion

Dr. Ravi Chari (Nashville, TN): Dr. Eisenberg, I would like to congratulate you and Dr. Fong on another excellent presentation, which continues a line of investigation with regard to oncolytic virus in the management of hepatobiliary malignancy. Your presentation was very thoughtful, but I must tell the membership that the paper is even more impressive and I enjoyed reading it and it provided a lot more information beyond what you showed today. I look forward to its publication. I have the following questions.

The first question centers on the virus selection. In both your presentation and manuscript you indicate that you selected NV1066. Previous work in hepatobiliary malignancy and specifically colorectal metastases to the liver has centered on NV1020. Could you outline the reasons why 1066 was chosen instead of 1020?

The second question has to do with your time-line of increased expression of GADD34. With regard to a clinical model or a more clinical appropriate scenario, administration of chemotherapy would probably follow viral administration. What impact would the rapid but short induction of this GADD34 have in a clinically relevant model where 5-FU is administered several weeks or days after the virus itself?

And finally, while you also just touch on it in your paper, I would ask you also to say in the scenario of clinical management of pancreatic cancer, how would you envision the use of NV1066?

Again, I enjoyed this presentation and paper and thank you.

Dr. Eisenberg: Thank you, Dr. Chari, for your kind comments. If I may answer your final question first, there are many clinical settings in which we can envision using these viruses in the treatment of patients with pancreatic cancer. In the preoperative setting, we can target patients with locally advanced disease where resection is not possible, delivering the virus directly into the tumor either via a percutaneous route under CT guidance or endoscopically with the hope of downstaging these patients to ultimately achieve a potentially curative resection.

Regarding intraoperative delivery, we have heard extensively this week that the retroperitoneal resection margin following pancreaticoduodenectomy is problematic and is the site of local recurrences in

a significant percentage of patients. Virus could be delivered locally into the retroperitoneum following resection of the pancreas in an attempt to sterilize this difficult margin.

Finally, these viruses could be administered in the adjuvant setting either regionally or systemically. As we have already heard this morning, recurrence patterns frequently involve the peritoneal surface and the liver. Both of these sites can be targeted regionally by delivery of virus into the peritoneal cavity or hepatic artery, respectively, and both routes have already been shown to be efficacious in experimental models of cancer in our laboratory.

Regarding your second question, these experiments were conducted by first briefly exposing cancer cells to a very low dose of 5-FU. What followed was GADD34 mRNA upregulation peaking at 24 hours and then falling off. We know from recent experiments in our laboratory that the protein level of GADD34, which is more accurately what we hypothesize the virus is exploiting resulting in the synergy that is observed, is upregulated well beyond that and at least out to 72 hours. As such, this work may favor administering chemotherapeutics prior to the delivery of virus. That being said, as long as there are viable, replicating viral particles within the tumor at the time of administration of chemotherapeutics, regardless of whether it is before or after viral administration, virus may be able to exploit the induced cellular stress response in cancer cells.

Finally, regarding the use of NV1066 versus NV1020, while we investigate many herpes viral strains in our laboratory, most of our experience is with G207 and NV1020, NV1020 being the strain that we used in our phase I clinical trial in patients with colorectal liver metastases. Using these viruses we have demonstrated synergy with mitomycin C in a gastric cancer cell line and with radiation in a colon cancer cell line. This synergism, however, is not universal in that it is not seen with some other cancer cell lines and other chemotherapeutic agents. So we used this opportunity to further explore to what extent this synergism exists across the range of our viruses. Additionally, NV1066 carries the enhanced green fluorescent protein transgene, which will enable us to track infection and monitor vector spread as we further investigate these pharmacologic interactions in vivo.

Dr. Mark Callery (Boston, MA): With respect to the clinical scenario, what would you see as the most likely reason why this would fail going forward? And also, I didn't fully understand the importance of the elongation and initiation factor. Are you trying to achieve a global translational repression of protein synthesis as part of the cell kill?

Dr. Eisenberg: Initial clinical trials demonstrated the safety and efficacy of direct local injection of these agents into tumors. After that, Dr. Fong was the first to inject these viruses into the bloodstream and showed that it was safe. Immunity was an initial concern considering that 90% of adults have circulating antibodies to the herpes virus. But animal studies looking at viral uptake and efficacy in preimmunized animals showed negligible attenuation when administered systemically versus regionally.

We are unbelievably excited about these viruses, but just as with any other anticancer agent, tumors are heterogeneous and tumor cells are very clever, and they certainly may find their way around these viruses just as they do chemotherapy and radiation. That being said, up to today, after testing over 110 cell lines in our laboratory, we have really found only several cell lines that are highly resistant.

With respect to the initiation factor, following a herpes viral infection, the host cell tries to shut off its own protein synthesis so the virus can no longer use that machinery to replicate. It does this by phosphorylating the alpha subunit of an initiation factor called eIF-2. Wild-type virus counters this defense mechanism by dephosphorylating that initiation factor which is a result of the viral gene gamma-1 34.5 and enables host cell protein synthesis and viral replication. NV1066, however, is attenuated by deletion of gamma-1 34.5. GADD34 is a host cell DNA repair enzyme that is highly homologous to viral gamma-1 34.5. So, we are trying to enhance viral replication by cancer cell–specific induction of GADD34 to bypass the viral attenuating deletion.

Dr. Michael Sarr (Rochester, MN): This study is really fascinating and shows my naivete on it, but tell me, where are you going to go with this? You theoretically can design where you want to impact the cell by what chemotherapeutic or radiotherapeutic agents you use. Although you have looked at one pathway, what other pathways are you going to explore?

Dr. Eisenberg: There are other pathways that we have looked at, and yes, essentially we are trying to modify these cancer cells to make them even more sensitive than they already are to these agents. In an earlier study, we looked at the gene ribonucleotide reductase. Ribonucleotide reductase is involved with the synthesis of DNA building blocks, the viral counterpart of which is deleted from the G207 virus for attenuation. We know that ribonucleotide reductase is upregulated following radiation of cancer cells which may benefit G207 viral replication in much the same way that GADD34 benefits NV1066. NV1066, however, doesn't have a mutation of ribonucleotide reductase and therefore isn't dependent

on it. That's why we didn't explore that pathway here. But, by identifying these mechanisms, we could theoretically take biopsies of tumors after a course of chemotherapy, assess the expression levels of these genes or proteins, and target a particular virus to a particular cancer.

An initial concern was that GADD34 upregulation in these cells may potentially make normal cells more vulnerable to viral infection. But published literature suggests that radiated fibroblasts with up to 20 Gy demonstrate negligible upregulation of GADD34. It appears that GADD34 is significantly more upregulated in cancer cells. Regardless, these viruses are attenuated via multiple mutations and therefore we would not expect to see viral replication in normal cells.

Dr. C. Max Schmidt (Indianapolis, IN): I enjoyed your talk very much. In your graphs where you look at cell growth, you talk about "cell kill." The reality is that the tumor cells in your control and treatment arms continue to grow since you have represented them as percent of control and all of the percents are positive. Is it truly "cell kill" or are your treatments just causing them to grow slower? If it is cell kill, have you looked at whether it is necrosis, apoptosis, or whether you are affecting the cell cycle?

Dr. Eisenberg: It is truly cell kill, the majority of which is due to direct cellular lysis, although work from our laboratory has also shown that there is likely a lesser component of apoptosis of infected and uninfected neighboring cells as well.

Current Practice Patterns in Pancreatic Surgery: Results of a Multi-institutional Analysis of Seven Large Surgical Departments in Germany With 1454 Pancreatic Head Resections, 1999 to 2004 (German Advanced Surgical Treatment Study Group)

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Despite decreasing mortality rates, morbidity is still high after pancreatic head resection. Comparative data in the United States and Europe show a relationship between hospital volume and mortality. Treatment strategies vary frequently, partially because of the lack of evidence-based data. We performed a multi-institutional analysis in Germany evaluating current numbers, indications, techniques, and complication rates of pancreatic head resection. Questionnaires were completed by seven high-volume surgical departments regarding quantitative and qualitative aspects of pancreatic head resections in the period from 1999 to 2004 (five prospective and two retrospective institutional databases). A total of 1454 pancreatic head resections (944 for malignancy) were reported. Mean annual hospital volume ranged from 14 to 52 (10 to 43 in malignancy). Mortality was between 1.1% and 4.8%, morbidity was between 24% and 46%, and pancreatic leakage was between 9% and 20%. In malignant disease, all centers perform standard lymphadenectomy and regard arterial infiltration as a contraindication for resection. However, the rate of portal vein resection varied from 0% to 28%. No consensus is seen on the type of surgery for malignancy and chronic pancreatitis. After resection for pancreatic cancer less than one fourth of the patients receive adjuvant therapy. The results of our analysis in Germany confirm that pancreatic head resection can be performed with low mortality in specialized units. Variations in indications, operative technique, and perioperative care may demonstrate the lack of evidence-based data and/or personal and institutional experience. The low number of patients receiving adjuvant therapy after resection of pancreatic cancer suggests that more efforts must be made to establish novel adjuvant therapies under randomized study conditions. (J GASTROINTEST SURG 2005;9:1080–1087) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Pancreatoduodenectomy, pancreatic cancer, chronic pancreatitis, hospital volume, postoperative complications

Pancreatic head resection (PHR) is still a surgical procedure with high complication rates. Once also associated with high mortality rates, pancreatoduodenectomy can now be performed with a perioperative mortality of clearly less than 5%, especially when undertaken in so-called high-volume centers or by high-volume surgeons as demonstrated by national comparative data from the United States and Europe.[1–4]

Because of the lack of or conflicting evidence-based data, there are still many controversies on surgical and perioperative treatment in pancreatic or periampullary cancers, as well as in chronic pancreatitis.

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To report the current techniques and results of PHR in Germany, the German Advanced Surgical Treatment (GAST) study group performed an analysis of PHRs performed between 1999 and 2004 in seven large surgical departments.

PATIENTS AND METHODS

The GAST study group was founded in 2004 by the chairmen of eight large general surgical departments (seven university departments and one academic teaching hospital) throughout Germany. The scientific aims of the study group are especially the creation of common large data sets of different surgical diseases and the initiation of large multicenter studies including randomized trials.

In a first step, parallel to the initiation of common prospective databases and trials, summary analyses of already established single institutional databases or retrospective series, respectively, were undertaken by the eight departments for different surgical entities. In this study we report the results of the analysis regarding pancreatic resections in the form of pooled summarized data of seven departments. In addition to numeric data, current technical and oncologic strategies were also evaluated.

Questionnaires with quantitative and qualitative questions regarding pancreatic resections performed between 1999 and 2003 were sent to the participating departments in September 2004. In March 2005, questionnaires analyzing the numbers of the year 2004 were sent again. After the initial evaluation of all pancreatic resections the questionnaires were focused on PHRs and included, among others, the following.

Quantitative: Annual numbers of different types of surgery (pylorus-preserving pancreatoduodenectomy, Whipple resection, Beger and Frey operations, distal pancreatic resection, and segmental central resection) for each malignant and benign disease; mortality after PHR; and morbidity (total, pancreatic leakage, bleeding, wound infection, and intraabdominal abscess) including reoperation, type and technique of pancreatic anastomosis, use of abdominal drains, and median length of postoperative hospital stay were asked. In regard to PHR for malignant tumors, we evaluated the percentage of the different tumor entities (pancreatic, ampullary, distal bile duct, or duodenal cancer), the percentage of superior mesenteric portal vein resection, and the type and percentage of lymphadenectomy. Furthermore, the type and frequency of neoadjuvant and adjuvant therapies after resection of pancreatic adenocarcinoma were asked.

Qualitative: In regard to all PHRs, we evaluated the perioperative use of octreotide and the definition of pancreatic leakage. In regard to malignant tumors, the diagnostic imaging modalities used in the preoperative workup were noted, as well as contraindications for surgery. For chronic pancreatitis, we further analyzed indications for surgery and the percentage of the different types of PHR performed over the whole 6-year period.

Because of different institutional databases, partially different definitions of complications, and the retrospective pattern in two departments, we could not explicitly focus on detailed analysis of postoperative complications such as delayed gastric emptying or some perioperative data such as estimated blood loss or transfusions.

Complete questionnaires containing each center's summarized data were obtained from seven departments. Five of them have prospective pancreatic surgery databases, and two gained the data retrospectively (Table 1). The data were then entered into a computerized database (SPSS, release 11.5, SPSS Inc., Chicago, IL) for further analysis.

RESULTS

From 1999 to 2004, a total of 1797 pancreatic resections were performed in the seven surgical departments. A total of 1454 PHRs were further analyzed.

All Pancreatic Head Resections (n = 1454)

The annual frequencies of PHRs by department varied between 10 and 61 (Table 2). The mean annual

Table 1. Participating surgical departments, type of data acquisition, and number of surgeons performing pancreatic head resections, 1999–2004

City	Institution	Database	No. of surgeons
Berlin	Charite Universitätsmedizin Campus Benjamin Franklin	Retrospective	4
Dresden	Technical University	Prospective	6
Essen	Alfried Krupp Krankenhaus	Retrospective	3
Freiburg	University Hospital	Prospective	4
Göttingen	University Hospital	Prospective	5
Mannheim	University Hospital	Prospective	6
Münster	University Hospital	Prospective	10
Total			**38**

Table 2. Annual numbers of all pancreatic head resections by department

Department	1999	2000	2001	2002	2003	2004	Total	Cases/ year
A	48	53	59	55	41	57	313	52.2
B	55	58	55	43	41	43	295	49.2
C	55	61	26	44	48	54	288	48
D	29	37	32	27	27	34	186	31
E	31	28	23	25	24	19	150	25
F	10	10	11	16	11	26	84	14
G	15	14	30	42	18	19	138	23
Total	**243**	**261**	**236**	**252**	**210**	**252**	**1454**	**34.6**

number (hospital volume) of PHRs per department over the 6-year period ranged from 14 to 52.

The mortality rates after PHR were between 1.1% and 4.8% and showed no obvious correlation to the caseload (Table 3). Overall morbidity was between 24% and 46% with pancreatic leakage occurring in 9% to 20% after PHR. The definitions of pancreatic leakage, however, varied: All institutions consider anastomotic insufficiency seen during reoperation and interventionally drained fluid collections with high amylase content uniformly as pancreatic leakage, but the classification of pancreatic fistulas as shown by high amylase output through the abdominal drains is used very differently with its definition of onset between the third and tenth postoperative day. The reoperation rate varied between 3% and 17%. The median postoperative length of stay was between 13 and 19 days (Table 3).

Reconstruction after pylorus-preserving pancreaticoduodenectomy (PPPD) or the Whipple procedure consisted of pancreatojejunostomy in almost all cases. In five of the seven departments, pancreatojejunostomy was performed exclusively. Pancreatogastrostomy was performed rarely in the remaining two institutions (in 9% and 4% after pancreatoduodenectomy) (Table 4). In regard to the anastomotic suturing technique, two of the seven departments performed pancreatojejunostomy with the duct-to-mucosa technique, whereas the other five performed the anastomosis between the jejunum and the whole pancreatic cut surface without the duct-to-mucosa technique.

All seven departments use abdominal drains in the perioperative management. Octreotide, however, is routinely applied in only three departments; octreotide is applied occasionally in three other departments, and perioperative octreotide is never given in one department.

Pancreatic Head Resection for Malignancy (n = 944)

The annual numbers of pancreatoduodenectomies for malignant disease by department were between 4 and 54 (Table 5) with an average hospital volume of 10 to 43 per year. The relative frequencies of indications for PD are shown in Table 6 with pancreatic and ampullary cancer being the two leading indications.

Tumor involvement of the visceral arteries (superior mesenteric and hepatic) is regarded as a contraindication for curative resection in all seven departments. Superior mesenteric-portal vein infiltration per se was seen as an absolute contraindication by only one department, whereas circumferential tumor involvement greater than 180 degrees was judged as an absolute or relative contraindication for resection by all responsible surgeons. The presence of local lymph node involvement was not regarded as an absolute contraindication.

The type of PD for malignant disease varied (Table 7). Four centers predominantly perform PPPD, whereas three prefer the classic Whipple procedure. All surgeons perform standard lymphadenectomy, that is, lymphadenectomy of the right upper quadrant not extending to the left side of the mesenteric root. Much variation was observed regarding the frequency of superior mesenteric-portal vein resection ranging

Table 3. Morbidity and mortality after pancreatic head resection, 1999–2004

Department	n	Mortality	Total morbidity	Pancreatic leakage	Reoperation	LOS (d)
A	313	3.2%	42%	11%	17%	19
B	295	4.1%	46%	10%	11%	13
C	288	2.1%	44%	15%	8%	15.5
D	186	1.1%	24%	10%	3%	15
E	150	1.3%	29%	15%	13%	17
F	84	4.8%	28%*	11%*	5%*	19
G	138	1.4%	35%*	20%*	6%*	17

LOS = median postoperative length of stay.
*Retrospective series.

Table 4. Type of pancreatic anastomosis after pancreatoduodenectomy

Department	Pancreatojejunostomy	Pancreatogastrostomy	Duct-mucosa technique
A	100%	–	92%
B	100%	–	–
C	91%	9%	4%
D	100%	–	100%
E	100%	–	–
F	96%	4%	–
G	100%	–	–

from 0% (the department that always regards vein involvement as a contraindication) to 28% (Table 7).

Adjuvant or Neoadjuvant Therapy in Pancreatic Cancer

Currently, only two of the seven departments include (few) patients into neoadjuvant chemoradiation if preoperative staging shows local irresectability of pancreatic head cancers. Only three departments suggest adjuvant therapy after curative resections (in two of them under study conditions). When all departments are combined, less than one fourth of the patients receive adjuvant treatment after resection of pancreatic head cancer.

Strategies in Chronic Pancreatitis

The indications for surgery for chronic pancreatitis are judged rather uniformly by the different departments. Intractable chronic pain, jaundice, and duodenal obstruction by chronic pancreatitis predominantly of the pancreatic head are regarded by all surgeons as indication for surgery. Compression or thrombosis of the portal venous system alone, without the other mentioned complications of chronic pancreatitis, is rarely regarded as indication for resection. Stenosis of the main pancreatic duct and pseudocysts without other clinical signs are rarely seen as indication for surgery.

Surgical techniques for chronic pancreatitis predominantly of the pancreatic head show much variation between the departments (Table 8). Three centers prefer PPPD, and two centers prefer duodenum-preserving techniques. It is of note that duodenum-preserving techniques are not used in two departments. Isolated pancreaticojejunostomy without resection is now rarely performed (Table 8).

DISCUSSION

Our multi-institutional analysis of PHRs is the first study of this kind in Germany and reports on more than 1450 PHRs performed in seven high-volume surgical departments during the last 6 years. It confirms national or regional data from the United States[1,2] and Europe,[3–5] as well as an increasing number of single-center series from specialized units[3,6–10] showing that PHR can be performed with a mortality rate less than 5%. When the data are analyzed from the national comparative studies in the United States[1] and The Netherlands,[3] at least five, if not all, of the participating departments of our analysis have to be classified as specialized pancreatic units. Further statistical analysis of volume-mortality relationship within our survey, therefore, was not

Table 5. Annual numbers of pancreatic head resections for malignant disease by department

Department	1999	2000	2001	2002	2003	2004	Total	Cases/ year
A	32	46	50	44	35	54	261	43.5
B	28	26	26	22	25	28	155	25.8
C	19	19	13	29	33	36	149	24.8
D	25	29	24	23	21	23	145	24.2
E	23	20	19	21	16	8	107	17.8
F	9	10	9	13	9	13	63	10.5
G	4	12	13	16	10	9	64	10.7
Total	**140**	**162**	**154**	**168**	**149**	**148**	**944**	

Table 6. Indications for pancreatoduodenectomy (malignant; n = 921)

Department	n	Pancreatic cancer (%)	Ampullary cancer (%)	Distal bile duct cancer (%)	Duodenal cancer (%)
A	261	70	10	10	5
B	155	50	31	15	4
C	149	55	16	16	2
D	122	79	18	2	1
E	107	60	20	15	5
F	63	73	20	1	6
G	64	76	10	7	7

Table 7. Operative strategies during pancreatoduodenectomy for malignant disease 1999 to 2004

Department	n	SMV-PV resection (%)	LAD	% PPPD	% Whipple
A	261	11	standard	90	10
B	155	16	standard	75	25
C	149	28	standard	88	12
D	145	3	standard	41	59
E	107	5	standard	93	7
F	63	10	standard	0	100
G	64	0	standard	29	71

SMV-PV = superior mesenteric–portal vein; LAD = lymphadenectomy; PPPD = pylorus-preserving pancreatoduodenectomy.

performed. Nevertheless, one may conclude from our data that beyond a certain annual number of PHRs, a further increase of the caseload does not result in a further decrease of postoperative mortality.

Our study also confirms that PHR still carries a relatively high risk of postoperative complications. Because of different definitions of postoperative complications and partially different data analysis, the complication rates are hardly comparable between the institutions and the literature, but the evaluation of complication rates was not a major end point of our analysis. Nevertheless, our results indicate that pancreatic leakage still represents a major part of complications after PHR even in experienced centers.

There is still not a uniformly used definition of pancreatic leakage, which makes comparison and analysis of this complication difficult. However, international efforts are currently made to establish a clinically relevant definition of pancreatic leakage by entering data into an Internet-based database (www.pancreaticdata.org).

Operative and Perioperative Techniques

There is an ongoing debate on the use of prophylactic octreotide to prevent pancreatic leakage with different results from randomized studies performed in the United States and Europe.[11–13] This open debate may be reflected in our survey because only three of seven departments routinely used octreotide prophylaxis.

In regard to octreotide prophylaxis, there is much controversial discussion on the type of surgery and anastomotic technique after pancreatoduodenectomy. Most specialized centers now perform PPPD, but others have abandoned this technique and "switched back" to the classic Whipple procedure because of a high rate of delayed gastric emptying after PPPD.[14] Pancreatojejunostomy was the most frequently used pancreatic anastomosis in our analysis and is certainly the technique preferred by most surgeons worldwide. The suture technique, however, has again come into discussion during the last years, probably because of the still relevant number of pancreatic fistulas. Although there are no results of randomized trials, some surgeons promote the use of a double-layer pancreatojejunostomy with duct-to-mucosa technique supported by very low rates of pancreatic leakage.[15] In our analysis almost all reconstructions were performed by using the jejunum, and only two of seven institutions performed a duct-to-mucosa anastomosis.

Strategies in Malignant Tumors

Two large randomized studies compared the outcome after PPPD and the classic Whipple procedure for malignant tumors. One study showed no difference between the operations;[16] in the other study, PPPD showed only some minor functional advantages during the early postoperative period.[17] These almost arbitrary results are reflected in our analysis because PPPD and the Whipple procedure were both performed for malignant tumors.

In regard to the extent of lymphadenectomy during PD for malignant tumors, there seems to be a clear consensus supported by two randomized studies showing that extended lymphadenectomy provided no survival benefit compared with standard

Table 8. Current operative techniques for chronic pancreatitis predominantly of the pancreatic head

Department	PPPD (%)	Whipple (%)	Beger (%)	Frey (%)	Pancreaticojejunostomy (%)
A	60	—	—	40	—
B	75	22	—	—	3
C	44	5	31	20	—
D	14	21	24	24	17
E	—	—	—	100	13
F	100	—	—	—	—
G	20	—	60	20	—

lymphadenectomy.[18,19] There was also a clear consensus that tumor invasion into the superior mesenteric or hepatic artery should be regarded as a contraindication for curative resection. Involvement of the superior mesenteric-portal vein, however, is judged controversially because contraindication for surgery is demonstrated by the large variations in the frequency of portal vein resection. There are no evidence-based data on the oncologic value of vein resection, but increasing data show that morbidity and survival are comparable in patients with or without vein resection.[10,12,13]

Adjuvant and Neoadjuvant Therapy in Pancreatic Cancer

Although the overall numbers of PD for pancreatic cancer have increased dramatically during the last two decades, there are still limited conclusive data on the role of adjuvant therapy. Recently the ESPAC-1 trial[20] showed a significantly higher survival rate after adjuvant 5-FU chemotherapy compared with the control group, but 5-year survival of the control group was low (10%), and the study was criticized because of its complex study design. Interesting results were published in a pilot study from Seattle in which the application of an interferon-alpha–based immunoradiochemotherapy showed dramatically improved survival rates after PD for pancreatic cancer.[21] Trials using this protocol are now also planned in Europe. It is rather surprising that only few patients in our analysis went to adjuvant therapy, despite the dismal prognosis of pancreatic cancer even after curative resection. This probably reflects the almost complete lack of evidence-based data (except the above mentioned) supporting any value of adjuvant therapy. Another potential reason for the low rate of adjuvant therapy may be the relatively high postoperative morbidity rate. However, their own experience[8] and the fact that most patients are discharged from the hospital within 3 weeks after surgery do not support this.

Strategies in Chronic Pancreatitis

The indications for surgery are seen relatively uniformly by all institutions. The types of surgery performed, however, vary with inconsistent use of duodenum-preserving techniques. This may also reflect the ongoing debate on resection for chronic pancreatitis. Although especially in the German-speaking parts of Europe, duodenum-preserving PHR is strongly promoted by some centers, these operations are rarely performed in the United States. Early studies from Germany found some advantages of duodenum-preserving PHR compared with PD,[22,23] but these were not confirmed in our large study from Rostock/Freiburg in which the long-term outcomes were equal after PPPD or duodenum-preserving PHR.[24]

CONCLUSION

The results of our analysis of seven large surgical departments in Germany confirm comparative data from other countries that PHR can be performed with low mortality in specialized units. Partially large variations in indications, operative technique, and perioperative care may demonstrate the lack of evidence-based data and/or good personal and institutional experience with the local treatment strategies. The low number of patients receiving adjuvant therapy after resection of pancreatic cancer in this analysis strongly suggests that more efforts must be made to establish novel adjuvant therapies under randomized study conditions. In view of the relatively large number of pancreatic resections performed by the members of the GAST study group, we can evaluate the possibility of common (randomized) studies.

The following participants (by department) contributed to the data acquisition: M. Niedergethmann, F. Willeke, S. Post (Department of Surgery, University Hospital Mannheim), F. Dobrowolski, H.D. Saeger (Department of Surgery, Technical University Dresden), F. Makowiec, E. Fischer, U.T. Hopt (Department of Surgery, University of Freiburg), M. Colombo-Benkmann, N. Senninger (Department of Surgery, University of Münster), B.M. Ghadimi, O. Horstmann, H. Becker (Department of Surgery, University of Göttingen), B. König, M. Betzler (Department of Surgery, Alfried-Krupp-Krankenhaus, Essen), A.J. Kroesen, H.J. Buhr (Department of Surgery, Charite, Campus Benjamin Franklin, Berlin).

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Discussion

Dr. L. William Traverso (Seattle, WA): Dr. Makowiec and colleagues have provided us with actual data from a large number of patients having pancreatic resection—these are actual data and not speculation. They were able to acquire these data because of trust. These eight German universities are linked together by a common key: They all trained together early in their career: therefore they all trust each other and are willing to share their data.

I think the ability to have more specific data from these eight German universities is the important aspect here because it has identified more specific items about pancreaticoduodenectomy and pancreatic head resections that we might not have known just using population-based studies such as those we have read in our literature by Birkmeyer. As you know, population-based studies have a higher number of patients than the usual hospital-based databases, but population-based studies have a low quantity of specific items. If a population-based database had more specific data then one would question its accuracy because it would not be doctor-derived. The GAST group provide both high-volume and specific data points that are doctor-derived.

Dr. Makowiec, now that you have done this initial trial, what are you planning to do next? Are you planning to expand the membership beyond eight German universities to others? Are you planning to expand the data points to those you have discovered are more pertinent? These could be estimated blood loss, the use of blood transfusions, the number of

readmissions, and the number of your cases of malignancy that were IPMN lesions? These are some of the unique aspects of pancreaticoduodenectomy that create specific benchmarks to assess the outcomes.

You also mentioned standardizing your definitions. What are you going to do about that? This study is like the Hawthorne effect: just by looking at the operation means the results are going to improve. Do you think the first step is to regroup, limit the number of data points to those that are valuable, and restandardize your definitions? You stated that you sent "questionnaires" to these participating institutions, but they really weren't questionnaires, were they? Weren't they downloads from already ongoing prospective databases that each of these German universities have? Questionnaires implies to me a request for a guess or a speculation, for instance, "estimate your incidence of morbidity." You actually acquired hard data that the institutions of the GAST group were already gathering. You were not just sending questionnaires? Is that correct?

Nice job by this cooperative effort of eight German universities.

Dr. Makowiec: Thank you for the comments. I think I will start with the final question about the questionnaire. It was not an excerpt from existing databases, but the data were created especially for our first GAST-members analysis. It contained quantitative questions for which the departments had to put in their annual numbers of the different operation types, but we also asked qualitative or semiquantitative questions, for example, about the indications for surgery or for certain types of surgery (e.g., answers were always, frequently, rarely, or never). We then also had fields where the departments could enter their percentages, for example, regarding the frequencies of the different tumor entities.

Regarding the inclusion of more hospitals into the GAST-group, it was the policy of the founders of the group to not include more hospitals before first obtaining reliable results to see whether our common data analysis system works.

In regard to your question on further databases, we created a computerized database that is concentrated on the more valuable items in our own prospective database from Freiburg, which has a large number of data fields. In this new database we especially ask for the complications with exact definitions (e.g., pancreatic leak, delayed gastric emptying). We also exactly analyze the histology of each patient including IPMN. It is still a very large database with about 200 fields per patient/operation and has already been sent to all members in January, and I hope in 2 years we have results of that.

Dr. Michael Schoenberg (Munich, Germany): I enjoyed your presentation, but two figures were exceptional. One institution resected the portal vein in nearly 30% of the patients. Do you think that this institution somewhat stretched the indication for resection? Interestingly, only 25% of all patients received adjuvant treatment. What were the reasons why 75% of all patients did not receive adjuvant treatment and/or were not included in adjuvant treatment studies?

Dr. Makowiec: We do not exactly know the reason for the large variation in portal vein resection. But this effect is well known from other regions when you compare, for example, the rather low rate of vein resections of the Johns Hopkins group with the almost 40% vein resection rate of the M.D. Anderson group. However, the indication in the group performing vein resection in 29% of their patients was certainly not stretched, because morbidity and mortality did not increase with vein resection, and free resection margins were obtained in 70% of those patients.

In regard to adjuvant therapy, we discussed that yesterday at the Pancreas Club meeting, and it seems that in the United States, in the leading centers, almost all eligible patients go to adjuvant therapy, often including radiation. But this is not the case in Germany. Except for the ESPAC-1 study, which can also be criticized, there is no evidence-based data on adjuvant therapy. Of course we should enter patients into studies, and our GAST study has pointed out how frequently studies are used.

Pancreas-Sparing Duodenectomy Is Effective Management for Familial Adenomatous Polyposis

Richard Mackey, M.D., R. Matthew Walsh, M.D., Raphael Chung, M.D., Nancy Brown, R.N., Andrew Smith, M.B.B.S., James Church, M.D., Carol Burke, M.D.

Duodenal adenocarcinoma remains the leading cause of cancer death in familial adenomatous polyposis patients following colectomy. Stratification based on Spigelman's criteria provides a means for determining therapy. Spigelman stage IV patients have been selected for pancreas-sparing duodenectomy. Twenty-one patients underwent resection between 1992 and 2004, with a mean age of 58 ± 11 years. The mean time from colectomy to duodenectomy was 27 ± 13 years. Invasive cancer was found in the distal duodenum in one patient. Operative time averaged 327 ± 61 minutes with a mean blood loss of 503 ± 266 ml. There was no mortality, and eight patients (38%) had 14 complications: six (29%) with delayed gastric emptying, four (19%) with biliary/pancreatic anastomotic leak, one with pancreatitis, and one with wound infection. There were two reoperations: one for delayed gastric emptying and one for an early biliary leak. Mean length of stay was 15 ± 10 days. Two late complications occurred: a stomal ulcer and an intestinal obstruction at 48 and 24 months, respectively. Mean follow-up was 79 months (range, 3–152 months). Two patients developed polyps in the advanced jejunal limb and were endoscopically treated. Pancreas-sparing duodenectomy represents a definitive treatment for advanced duodenal polyposis and can obviate the need for pancreaticoduodenectomy. (J GASTROINTEST SURG 2005;9:1088–1093) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Pancreas-sparing duodenectomy, pancreaticoduodenectomy, familial adenomatous polyposis

Duodenal cancer is the leading cause of cancer related death in patients with familial adenomatous polyposis (FAP) who have undergone colectomy. Over 90% of patients will develop adenomatous duodenal polyps, yet only 5% progress to cancer.[1] Therefore, it is important to stratify patients by disease severity to better predict outcome. The classification system of duodenal disease by Spigelman and colleagues[2] segregates patients based on number, size and histopathology. The stages range from I to IV, with IV representing the most advanced stage where 36% will develop carcinoma.[1] Endoscopy is essential for initial staging and surveillance to assess stage migration. Surveillance of the upper gastrointestinal tract typically begins 1–2 years after colectomy. The incidence of stage IV disease on the initial endoscopy is 7%, while progression may occur in 30–52% by 70 years of age.[3,4] Surgical intervention for FAP patients with duodenal polyposis has ranged from endoscopic ablation to pancreaticoduodenectomy. Local therapy, endoscopic or surgical, may be appropriate for minimal, early-stage disease, but recurrence rates up to 100% after local resection do not represent definitive management of FAP and do not alter disease progression.[5–8] Pancreaticoduodenectomy or pancreas-sparing duodenectomy (PSD) should both offer definitive therapy in preventing duodenal carcinoma. PSD has been used infrequently for the management of FAP, although it offers the potential advantage of preserving normal pancreas without additional morbidity.[9–11] We have reviewed our experience with PSD to assess perioperative morbidity and long-term disease outcome.

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PATIENTS AND METHODS

Twenty-one consecutive PSDs performed between 1992 and 2004 at the Cleveland Clinic Foundation were reviewed. All patients were participating in an upper gastrointestinal surveillance program led by the Department of Gastroenterology or at an outside institution.[12] All patients were diagnosed with FAP and had previously undergone colectomy. Spigelman stage IV disease was present in 19 patients, one of whom presented with intussusception from a polyp in the fourth portion of the duodenum. The remaining two patients, one stage II and one stage III, were offspring of a PSD patient and opted for early resection.

Preoperative endoscopy is necessary to classify patients into Spigelman stage. Both end and side-viewing duodenoscopy are essential and routinely performed in surveillance endoscopy. Biopsies are typically obtained from an abnormal ampulla, duodenal polyps greater than 1 cm, or any additional concerning polyps. Biopsies of the periampullary region are not routine if the ampulla remains normal.

Routine preoperative imaging studies included computed tomography or magnetic resonance imaging to exclude desmoids, enteroclysis to evaluate the one remaining small bowel for polyps, and, more recently, magnetic resonance cholangiopancreatography for pancreatic divisum.

Institutional review board approval was obtained, and the data were collected via chart review. A PSD database was created and focused on the demographic, operative, and outcome data. Points of interest included age, gender, diagnosis, time from diagnosis to surgery, stage at initial endoscopy, number of endoscopies, duration of surveillance, endoscopic interventions, prior duodenal surgery, Spigelman classification at time of referral, length of stay (LOS), intensive care unit stay, duration of operation (defined from incision to closure), estimated blood loss (EBL), presence of desmoids, final pathology, immediate and late complications, postoperative endoscopic surveillance, recurrent polyps, duration of follow-up and survival.

Complications were divided into immediate, occurring within 30 days of operation, and late, which occurred thereafter. Pancreaticobiliary anastomotic leak was defined by drain amylase levels three times serum after the fifth postoperative day or bilious output from the surgically placed drains. Delayed gastric emptying was defined as the intolerance of a regular diet by the 10th postoperative day.[13] Follow-up was obtained through chart review of clinic visits, endoscopic surveillance reports, and direct patient contact.

Comparisons of morbidity were made between patients undergoing PSD and those undergoing pylorus-preserving pancreaticoduodenectomy (PPPD). It is recognized that these are disparate groups based on underlying pathology, but an attempt was made to compare outcomes at the same institution for the competing surgical alternative to PSD. Statistical analyses were not performed on these comparisons due to the heterogeneity of these patient groups.

Surgical Technique

Surgical exploration is performed typically through the patient's prior midline incision. The abdomen is explored to identify evidence of metastatic disease. The duodenum is widely Kocherized, exposing the inferior vena cava and third portion of the duodenum. The pancreatic head and papilla are palpated for evidence of tumor. Identification of the papilla is aided by passage of a catheter via the cystic duct after performing a cholecystectomy. The site of division in the proximal jejunum is determined either by the preoperative studies or intraoperative endoscopy when necessary. The proximal duodenum, approximately 2 cm distal to the pylorus, is divided with preservation of the proximal blood supply: the right gastric, the right gastroepiploic vessels, and the gastroduodenal artery. The distal stomach can be mobilized without division of these vessels for a tension-free anastomosis. The duodenum is transected distally and completely removed from the pancreas by carefully ligating the bridging vessels, leaving only the ampullary complex attached. The ampullary complex is typically posterior and is transected with needlepoint cautery to ensure a complete excision. The minor papilla is transected with the same technique but is suture ligated if it is clearly identified. The duodenal specimen is opened: the ampulla is identified with a suture and frozen sections are obtained from both the ampulla and the largest duodenal polyp.

Reconstruction is then performed with an advanced jejunal limb. An end-to-side pancreaticojejunostomy is completed first, followed by an end-to-end or end-to-side duodenojejunostomy (Fig. 1). The pancreatic and biliary orifices are reconstructed via one enterotomy with a single layer of interrupted absorbable sutures. Eight patients underwent an alternative technique consisting of reimplantation by an intra-jejunal approach via a separate enterotomy.[9] A 5F internal pancreatic duct stent is always used, and an assessment for pancreatic divisum is performed by its passage into the pancreatic body. In the case of divisum, a separate enterotomy and a duct-to-mucosa anastomosis are performed in similar fashion with interrupted sutures over a stent. All

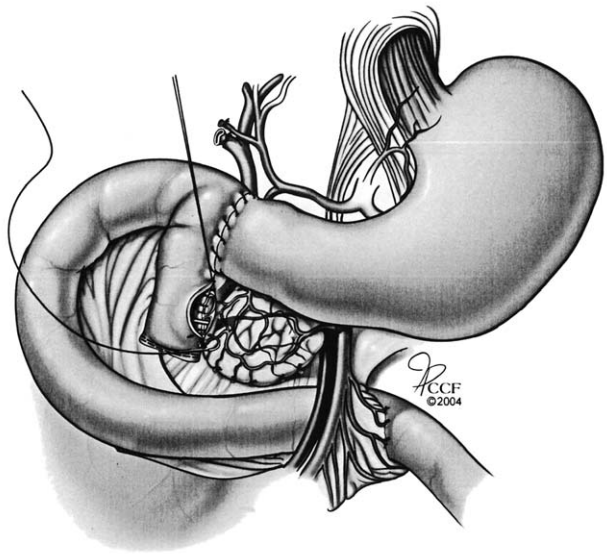

Fig. 1. Schematic representation of PSD reconstruction using an advanced jejunal limb and completed end-to-side pancreaticojejunostomy and end-to-side duodenojejunostomy (occasionally end-to-end duodenojejunostomy is performed based on limb configuration).

patients underwent endoscopy for stent removal approximately 2 months after operation. A nasojejunal feeding tube is placed and secured.[14]

RESULTS

PSD was performed in 21 patients with FAP between 1992 and 2004, representing approximately 11% of the patients undergoing endoscopic surveillance at the Cleveland Clinic. Two additional patients were referred for PSD but were found to have invasive carcinoma. The first patient had an ampullary carcinoma identified at operation and underwent a pancreaticoduodenectomy, and the other patient had metastatic disease on preoperative evaluation. There were 15 men (71%), and the mean age at operation was 58 years (range, 37–76 years). The mean time from colectomy to PSD was 27 years (range, 7–55 years). Six patients presented with Spigelman IV disease at the initial endoscopy and underwent PSD without further surveillance. The remaining patients consisted of 3 stage III, 10 stage II, and 2 stage I patients and were surveyed for a mean of 82 months (range, 7–216), receiving an average of 10 (range, 2–38) endoscopic procedures prior to resection.

Prior endoscopic and surgical procedures performed included four patients who underwent endoscopic polypectomy, two patients who underwent repeated bicap/heater probe ablations, three patients who underwent transduodenal polypectomy, and one patient who required exploration and duodenal repair after an endoscopic perforation. The transduodenal polypectomies were performed for solitary, large polyps not in proximity to the ampulla.

All 21 PSDs were performed by two surgeons at the Cleveland Clinic Foundation (R.M.W. and R.C.). Only one patient was symptomatic with a large 4-cm obstructing polyp intussuscepting in the fourth portion of the duodenum. Eleven patients had severe dysplasia on preoperative biopsy. Operative pathology revealed tubulovillous adenoma in 20 patients. The patient that presented with intussusception had invasive carcinoma in the fourth portion of the duodenum and one positive periduodenal lymph node. All of the intraoperative frozen section specimens of the ampulla were negative for carcinoma. Desmoid tumors were encountered in three patients, one of which was resected. There were no deaths.

Complications occurred in eight patients with the most common being delayed gastric emptying in six patients (29%). A combination of gastric decompression, prokinetic agents, and temporary enteral nutrition was successful in five patients. One patient required reoperation and a gastrojejunostomy at 2 weeks. Exploration revealed obstruction of the jejunal limb and a tethered mesentery just distal to the ligament of Treitz secondary to a desmoid tumor. A pancreaticobiliary leak occurred in four patients. One patient developed a leak within 24 hours and was successfully managed with reexploration, proximal biliary decompression with a T-tube, and anastomotic drainage. The other anastomotic leaks were successfully managed with closed suction drains placed at the original operation, parenteral nutritional, and bowel rest. There was one patient who developed a postoperative wound infection that healed by secondary intention. Finally, one patient developed pancreatitis in the early postoperative period, and follow-up endoscopic retrograde cholangiopancreatography (ERCP) demonstrated no evidence of an anastomotic stricture. Two late complications occurred: One patient developed a stomal ulcer at 48 months, and another presented with an intestinal obstruction at 24 months, requiring enterolysis.

Selected perioperative factors including operative time, blood loss, complication rates, LOS, and survival were compared with outcomes after PPPD at our institution (Table 1). Patients underwent PPPD for various pathologic reasons including pancreatic cancer, chronic pancreatitis, ampullary neoplasms, cholangiocarcinoma, duodenal carcinoma, intraductal papillary mucinous neoplasms (IPMNs), and FAP-related disease with identified carcinoma.

Table 1. Perioperative Outcomes of PSD and PPPD

	PSD (n = 21)	PPPD (n = 238)
Age (yr)	57.7 ± 10.6	63.3 ± 13.4
OR time (min, mean)	327 ± 61	370 ± 84
EBL (ml, mean)	503 ± 266	NA
Complications	14 (38%)	141 (43%)
DGE	6 (29%)	44 (18%)
Leak	4 (19%)	22 (9%)
Other	4 (18%)	75 (32%)
Reoperation	2 (9.5%)	NA
LOS (days, mean)	14.6 ± 9.8	14.3 ± 11.5
Mortality	0 (0%)	3 (1.3%)

PSD = pancreas-sparing duodenectomy; PPPD = pylorus-preserving pancreaticoduodenectomy; OR = operative time; EBL = estimated blood loss; LOS = length of stay; DGE = delayed gastric emptying; NA = not available.

These data points were prospectively collected over the past 10 years for all patients undergoing PPPD and provide imprecise reference points for the comparison to PSD, especially given the disparate pathology. The operative time was longer in the PPPD cohort and is likely multifactorial. The overall complication rates of 38% and 43% for PSD and PPPD, respectively, were similar. Postoperative morbidity included delayed gastric emptying (29% versus 18%) and anastomotic leak rates (19% versus 9%) were similar. The LOS (14.6 versus 14.3 days) was similar, and the perioperative mortality for PSD and PPPD were 0% and 1.6%, respectively. For PSD, the EBL averaged 503 ± 266 ml. Postoperatively, two patients were admitted to the intensive care unit for 1 day.

Clinical and endoscopic follow-up was achieved in all patients undergoing PSD for a mean of 79 months (range, 3–152 months). Two patients developed adenomatous disease in the reconstructed limb. The first patient had a 4-cm polyp in the advanced jejunum and minimal biopsy-proven adenomatous tissue adjacent to the neoampulla at 68 months. The larger lesion was removed in a sequential, endoscopic piecemeal fashion and was shown to be tubulovillous adenoma. The second patient developed adenomatous polyps in the advanced jejunal limb near the duodenal cuff at 96 months, which were endoscopically resected. Surveillance endoscopy continues to show adenomatous disease in both patients, but there has been no progression in histology or dysplasia.

DISCUSSION

Management of duodenal disease in FAP patients must be directed at preventing duodenal carcinoma and ensuring good functional outcome. We have used the Spigelman classification system to guide our management approach, reserving definitive treatment for patients at highest risk for invasive cancer.[1–3,4] Stage IV disease has a 36% risk of carcinoma within 10 years.[1] The outcome of FAP patients who develop invasive cancer is dismal,[15] and this has fostered consideration of a more aggressive strategy for stage IV disease. Local endoscopic or surgical therapy is inadequate, and expected recurrence and potential progression approach 100%.[5,6,15] Only pancreaticoduodenectomy or PSD represents definitive treatment for stage IV disease. Our patient cohort of PSD represents the largest yet reported and should provide a useful facsimile for its utility. Analysis of our perioperative data suggests that it can be performed safely and without mortality. The overall morbidity of 38% and LOS of 14 days are comparable to our own experience with PPPD, although recognizing the disparate pathology treated in the latter patient group. It is perhaps most illustrative to compare our outcomes with a recent series of stage IV FAP patients treated by PPPD as reported by Gallagher et al.[15] The operative outcome in those 16 patients included mortality in 2 (12%) and morbidity in 8 (50%), median hospital stay of 36 days, and several late deaths resulting in nine survivors at a mean follow-up of 38 months.[15] Thoughtful reflection on these results may lead to reconsideration of the role of any definitive therapy or, conversely, the need for definitive options other than PPPD for stage IV disease.

The potential morbidity of PSD is not insignificant and principally involves delayed gastric emptying followed by a leak at the combined pancreaticobiliary anastomosis. Delayed gastric emptying can be a vexing short-term problem that is known to occur after pancreaticoduodenectomy, and it is not surprising that it could occur after PSD. Delayed gastric emptying occurs after both PPPD and the classic Whipple procedure, although it has been speculated to occur more frequently after PPPD.[16,17] Pylorus preservation appears to show an advantage to long-term quality of life following pancreaticoduodenectomy,[18] and we have favored its use with PSD to maintain satisfactory bowel function postcolectomy. The occurrence of DGE is the main contributor to our 14-day LOS, which is also similar to our LOS following PPPD. DGE is multifactorial, although removal of the duodenum and subsequently the peptide motilin are likely contributors. The relatively high propensity for DGE after PSD does highlight the need for postoperative enteral support, which we favor by secured nasojejunal feeding.[14]

An anastomotic leak is a potentially dire complication following PPPD or PSD. It can lead to reoperation, intra-abdominal abscess, sepsis, and delayed

strictures. In our series, all leaks were detected by operatively placed drains, and although one patient required early reoperation, the other three were managed as controlled fistulas and delayed outpatient drain removal without any intra-abdominal sepsis. Although PPPD necessitates an additional anastomosis compared with PSD, the major morbidity following both procedures is a leak from the pancreatic anastomosis. The overall incidence of pancreatic leak is expected to be 12–14% based on results from major centers.[16,17,19] However, the majority of patients in these series have an obstructed pancreatic duct from carcinoma or chronic pancreatitis, and therefore there is little relevance in predicting the leak rate following PPPD for a comparable group of patients who would undergo PSD. Pancreatic leak rates as high as 23% have been reported by several series following a duct-to-mucosa anastomosis or invagination of a pancreatic remnant of normal consistency.[20–22] We do believe that the incidence of anastomotic leak can be diminished through increased experience and attention to the technical details of a wide mucosa–mucosa, tension-free anastomosis. Factors directly related to PSD in this patient cohort that may contribute to an increased leak rate include the higher volume of pancreatic secretion with preservation of the whole gland, the potential disadvantage of mixing bile and pancreatic secretions at one anastomotic site, and the tethering of the mesentery in those patients with mesenteric desmoids.

An important consideration in assessing the utility of PSD is the long-term outcome, and our mean follow-up of 79 months is especially valuable. The full-thickness, complete duodenal resection achieved by PSD results in the potential recurrence sites at the distal pancreatic and bile duct, the duodenal cuff, and in the remaining jejunum and ileum. Recurrence of adenomatous tissue or carcinoma at the neoampulla is the only long-term potential disadvantage of PSD compared with PPPD. Biopsy-proved adenomatous disease has occurred at the neoampulla in one patient who also has extensive jejunal disease, including a 4-cm polyp in the advanced jejunum. It is suspected he will develop carcinoma at some location in his small intestine but not necessarily at the neoampulla.

It does appear that PSD is effective at preventing duodenal carcinoma, even at the ampullary complex. Previous small series of PSD have reported no neoampullary recurrence and jejunal polyps in 0–33% with comparatively short follow-up of 2–5 years.[4,5] Our reconstruction achieved by PSD does allow complete endoscopic postoperative assessment of the proximal jejunum, which would be more difficult following PPPD. Because resection of the duodenum shifts the carcinoma risk to the remaining small bowel, PSD does not obviate the need for continued endoscopic surveillance. Carcinoma in the duodenal cuff has been reported in an FAP patient 1 year following PPPD for an ampullary carcinoma, further highlighting the need for surveillance and endoscopic therapy.[23] The use of frozen section sampling at the time of PSD appears to be an effective strategy. All patients with negative frozen sections of the ampullary margin and the largest polyp at resection were found to have benign adenomatous disease at final pathology. One patient was suspected to have an ampullary carcinoma during palpation at the initial exploration and a PPPD was performed. The one patient with carcinoma in the fourth portion of the duodenum was treated with PSD and would not have benefited from PPPD.[13,24]

CONCLUSION

PSD offers definitive treatment of stage IV duodenal polyposis in patients with FAP. It has acceptable perioperative morbidity compared with patients undergoing pancreaticoduodenectomy. Post-resection endoscopic surveillance is necessary for ongoing assessment of the proximal jejunum.

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Discussion

Dr. Michael Sarr (Rochester, MN): I think you have shown us that you can do the operation safely, you had fewer complications than we did, but more importantly, you can survey these patients easily, and the disease, if it comes back, can be seen endoscopically, and should be able to be treated endoscopically. So this is a huge advance. I will gently caution you against comparing these patients with your pylorus-preserving resections, who probably had cancer and were thus relatively immunosuppressed. They are not a good comparison group.

I have two questions. First, you do not do a pre-op ERCP. How do you deal with these patients who have primarily peri-Vaterian and periampullary adenomatous disease? How are you sure that it is not creeping up the duct?

And second, in your manuscript you talk about the concern about Santorini's duct in those patients who have pancreas divisum. Tell us a little bit about how many people had divisum and how you dealt with the Santorini's duct.

Dr. Mackey: Thank you, Dr. Sarr, for your review and questions. In regard to the first question, a few of the patients early on underwent preoperative ERCPs, but it was not standard practice. Currently, we obtain MRCPs, which has two benefits: one, to define their pancreatic ductal anatomy, and the second is to identify mesenteric desmoid tumors.

Intrapapillary adenomatous tissue that may creep up the duct is certainly a concern. The ampullary complex is transected high in the pancreatic parenchyma. We did have one patient with adenomatous tissue extending up into the bile duct, and we continued the resection until the margin was negative. If the ductal disease extends through the pancreas, a more extensive resection may be required.

One patient had pancreatic divisum, which was identified and dealt with at the time of the operation. The pancreatic stent did not pass into the pancreatic body. We do place a longer suture on the minor papilla, and if in fact the pancreatic stent does not pass, we then open the minor papilla and reimplant it through a separate anastomosis.

Dr. William Nealon (Galveston, TX): With normal pancreas, at times you can have an early postoperative pancreatitis. You didn't mention that. Did you have any who you suspected may have had pancreatitis in their early postoperative period?

Dr. Mackey: We did. One patient developed early postoperative pancreatitis which resolved spontaneously. The patient had a follow-up ERCP and had no evidence of a stricture at the anastomosis.

Pancreaticoduodenectomy After Placement of Endobiliary Metal Stents

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Contemporary treatment programs for patients with potentially resectable pancreatic cancer often involve preoperative therapy. When the duration of preoperative therapy exceeds 2 months, the risk of plastic endobiliary stent occlusion increases. Metal stents have much better patency but may complicate subsequent pancreaticoduodenectomy (PD). We evaluated rates of perioperative morbidity, mortality, and stent complications in 272 consecutive patients who underwent PD at our institution from May 2001 to November 2004. Of these 272 patients, 29 (11%) underwent PD after placement of a metal stent, 141 underwent PD after placement of a plastic stent, 10 had PD after biliary bypass without stenting, and 92 had PD without any form of biliary decompression. No differences were found between the Metal Stent group and all other patients in median operative time, intraoperative blood loss, or length of hospital stay. No perioperative deaths occurred in the Metal Stent group versus 3 (1.2%) deaths in the other 243 patients. The incidence of major perioperative complications was similar between the two groups, including the rates of pancreatic fistula, intra-abdominal abscess, and wound infection. Furthermore, there were no differences in the perioperative morbidity or mortality rates between patients who underwent preoperative biliary decompression with a stent of any kind (metal or plastic) and those patients who underwent no biliary decompression at all. Metal stent-related complications occurred in 2 (7%) of 29 patients during a median preoperative interval of 4.1 months; in contrast, 75 (45%) of the 166 patients who had had plastic stents experienced complications, including 98 stent occlusions, during a median preoperative interval of 3.9 months ($P < 0.001$). We conclude that the use of expandable metal stents does not increase PD-associated perioperative morbidity or mortality, and as such an expandable metal stent is our preferred method of biliary decompression in patients with symptomatic malignant distal bile duct obstruction in whom surgery is not anticipated, or in whom there is a significant delay in the time to surgery. (J GASTROINTEST SURG 2005;9:1094–1105) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Pancreaticoduodenectomy, metal stent, biliary decompression

Controversy persists regarding the role of preoperative biliary decompression before pancreaticoduodenectomy (PD). Several retrospective studies have suggested that the placement of biliary stents increases perioperative morbidity[1–3] and mortality[1] in patients who subsequently undergo PD. A report from our institution showed that preoperative biliary decompression increased the rate of postoperative wound infection, but not the rates of pancreatic fistula, intra-abdominal abscess, or mortality, after PD.[4] Irrespective of this controversy, the placement of endobiliary stents before definitive surgery in patients with malignant distal bile duct obstruction has become increasingly common for several reasons. First, given the lethality of pancreatic cancer, greater emphasis has been placed on multidisciplinary treatment, including the delivery of preoperative therapy.[5] Second, patients often enter the health care system via gastroenterologists who may not specialize in the treatment of pancreatic cancer and

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thus may not be aware of the latest stage-specific treatment options for patients with pancreatic cancer. In such situations, placement of a plastic stent is a safe, if not always appropriate, approach. Third, definitive surgery is often delayed by the time required for referral to a high-volume center for primary treatment or for seeking second opinions. Surgery can also be delayed by the complexity of the surgery schedule and by the paucity of available operative time at many institutions. Finally, as the population ages, more patients are presenting with significant medical comorbidities that require particularly comprehensive preoperative evaluation.

Over the past 15 years, we have maintained an active clinical research program studying the multimodality treatment of localized pancreatic cancer and have enrolled patients in several clinical trials involving neoadjuvant chemoradiation.[6–8] Early trials of preoperative therapy involved a preoperative interval (i.e., the time interval between disease staging and operation) of approximately 2 months, and plastic stents provided adequate biliary decompression with few stent-related complications during this interval of time.[9] The evolution of our protocol-based treatment regimens and the finding that the predominant pattern of failure is distant (liver) metastases have led to an increase in the duration of preoperative systemic therapy. In our current clinical trial for potentially resectable pancreatic cancer, preoperative therapy lasts approximately 3 months and is followed by a 1-month recovery period before surgery. As a result of the increase in the preoperative interval from 2 to 4 months, we have witnessed an increased rate of plastic stent occlusion complicating the delivery of preoperative therapy. Given the superior long-term patency of metal stents compared with that of plastic stents,[10,11] we began placing endobiliary self-expandable covered metal stents to maintain biliary decompression in patients undergoing preoperative therapy. However, little published evidence is available on whether placement of endobiliary metal stents affects the success of PD or the rates of perioperative morbidity and mortality.

The objectives of this study were to determine whether preoperative biliary drainage with a metal stent complicates subsequent PD and to compare the rates of PD-associated morbidity and mortality among patients with an indwelling endobiliary metal stent, a plastic stent, or no biliary decompression at all. We also assessed the duration of stent patency, the incidence and type of stent-related complications, and the economic impact of maintaining preoperative biliary decompression with metal stents compared with plastic stents.

PATIENTS AND METHODS

We identified 272 consecutive patients from a prospective pancreatic tumor database who underwent PD for any histologic diagnosis between May 2001 (the date of the first PD for a patient with a metal stent) and November 2004 at The University of Texas M. D. Anderson Cancer Center. Patients who underwent total pancreatectomy or distal pancreatectomy were excluded from the analysis. A previous report from our institution describing our initial experience with metal stents in patients with resectable pancreatic cancer included 47 (17%) of these 272 patients.[12]

Preoperative Assessment and Treatment

Preoperative evaluations included physical examination, routine laboratory testing, chest radiography, and dual-phase, contrast-enhanced, thin-section, multidetector helical computed tomography (CT). All cases met objective radiographic criteria for resectable disease.[13] Most of the patients with biliary obstruction underwent biliary decompression to facilitate protocol-based preoperative therapy; the indications for preoperative biliary decompression were not considered in this analysis. Preoperative biliary drainage was achieved by endoscopic placement of a 10-Fr or 11.5-Fr plastic (polyethylene) stent or a 10-mm diameter, self-expandable covered metal Wallstent (Microvasive; Boston Scientific, Natick, MA) or, rarely, by placement of a percutaneous transhepatic catheter. Surgical biliary bypass procedures performed before definitive PD (and before referral to our institution) consisted of choledochojejunostomy, choledochoduodenostomy, or cholecystojejunostomy.

Preoperative chemoradiation was delivered on- or off-protocol as either standard-fractionation (50.4 Gy in 28 fractions) or rapid-fractionation (30 Gy in 10 fractions) external-beam radiation therapy given concomitantly with 5-fluorouracil, paclitaxel, or gemcitabine.[6,8,14] Some patients were also given chemotherapy before or after chemoradiation.

Pancreaticoduodenectomy Technique

All patients underwent preoperative bowel preparation with a polyelectrolyte solution with or without oral antibiotics. All patients received perioperative intravenous antibiotic prophylaxis consisting of a second-generation cephalosporin with or without metronidazole; patients allergic to penicillin were given ciprofloxacin and metronidazole. PD was performed in a standard fashion as described elsewhere.[13] When possible, a soft 12-mm occluding

bulldog clamp (Soft Surgical Spring Clip; Applied Medical Resources, Laguna Hills, CA) was positioned across the transected common hepatic duct to minimize intraperitoneal accumulation of bile until biliary-enteric continuity was restored by end-to-side hepaticojejunostomy. The use of surgically placed intra-abdominal drains became less common over the study period, such that by the end of 2002 surgical drains were no longer routinely placed near the pancreaticojejunal anastomosis.

Postoperative care was delivered according to a previously described clinical pathway.[15] Patients with unexplained postoperative fever, leukocytosis, or worrisome findings on physical examination underwent abdominopelvic CT scanning. When deemed appropriate by the attending surgeon, intra-abdominal fluid was drained percutaneously; aspirated fluid samples were sent for culture and biochemical evaluation for amylase level. Hospital stay was calculated by considering the day of surgery as day 1, and the day of discharge was not counted as a hospital day.

Operative Details and Perioperative Complications

Operative details recorded included the surgical time and intraoperative blood loss (as recorded in the anesthesia record), intraoperative transfusion of red blood cells, and details of the surgical procedure itself, including the need for concomitant vascular resection and reconstruction.[16] Major postoperative complications were defined as previously described[4] and included perioperative death (death within the first 30 days after surgery or during the hospital stay for surgery); need for reoperation; intra-abdominal hemorrhage; intra-abdominal abscess (postoperative fluid collection with positive fluid culture results); intra-abdominal sterile fluid collection; clinically evident pancreaticojejunal anastomotic leak or fistula (defined as a drain amylase level >2.5 times the upper limit of normal for serum amylase and at least one of the following: fever, leukocytosis, or intraabdominal fluid collection); other anastomotic leaks (from the biliary-enteric or gastrojejunal anastomoses); myocardial infarction; cardiac arrhythmia; pulmonary complications including pneumonia and pulmonary embolism; sepsis syndrome (positive blood cultures in the presence of fever without apparent source); and gastrointestinal bleeding. Of note, pancreatic anastomotic leaks or fistulas would not be clinically evident if percutaneous drainage or reoperation were not needed because the pancreatic anastomosis was rarely drained.

Minor complications recorded included central venous catheter infection, allergic reaction, wound infection, delayed gastric emptying (gastrostomy tube output >1 L on postoperative day 7 or inability to tolerate a postgastrectomy diet by postoperative day 10), chyle leak, drain complication, deep vein thrombosis, urinary tract infection (documented by positive urine culture), and infectious colitis (as documented by *Clostridium difficile* toxin assay).[4]

Stent-Related Complications and Cost Analysis

Stent patency was measured as the length of time from stent placement until one of two endpoints: stent occlusion or PD. The preoperative interval was measured from the time of stent placement to surgical resection and included the length of time for which biliary decompression was required to complete all preoperative evaluation and treatment.

Details of stent-related complications were obtained from the procedure note dictated by the endoscopist at the time of stent exchange and included stent occlusion, stent migration, hemobilia, and bile duct perforation. Stent occlusion was determined by injection of contrast via the stent (occlusion cholangiogram) or by evidence of occlusion of the distal lumen of the stent by debris. Details of hospitalizations for the management of biliary stent complications, most commonly cholangitis, were obtained from the medical records and included number of admissions to M. D. Anderson Cancer Center along with the recorded length of hospital stay.

A cost analysis was undertaken to assess the economic impact of maintaining preoperative biliary decompression with an expandable metal stent compared with a plastic stent. Economic data were retrieved from our patient billing database and listed as the current charges for all items and services as of May 2005. Charges were determined for the plastic and covered metal stents, the guide wires and fluoroscopy necessary for stent insertion or exchange, endoscopic retrograde cholangiopancreatography with stent exchange, 1 hour of monitored anesthesia, and endoscopy recovery room costs. Charges related to an emergency admission for symptomatic stent dysfunction were also determined, including the charges for an emergency center visit, a private inpatient hospital room for 24 hours, and provision of intravenous fluids and antibiotics for a 24-hour period.

Statistical Analysis

Results are expressed as medians and ranges or as numbers and percentages of patients. Univariate comparisons of all categorical variables were

performed by χ^2 analysis. Independent *t*-tests and Mann-Whitney *U* tests were used to evaluate continuous variables. A value of $P < 0.05$ was considered statistically significant. Variables determined to be statistically different between groups by univariate analysis were to be examined in multivariate analyses.

RESULTS

Clinicopathologic Characteristics

Of the 272 consecutive patients who underwent PD at our institution, 180 (66%) required preoperative biliary decompression: 170 patients underwent endobiliary stent placement, including three of the 13 patients who underwent biliary bypass procedures before referral to M. D. Anderson. Biliary stents were placed endoscopically in 164 patients, by the percutaneous transhepatic route in 14 patients, and by both routes in 8 patients.

A metal endobiliary stent was in place at the time of PD in 29 (11%) of the 272 patients, representing 18% of the 164 patients who had undergone endoscopic biliary stent placement. Twelve of these 29 patients with metal stents were previously included in an initial brief report from our institution.[12] A total of 166 (61%) patients had had biliary decompression with one or more plastic stents before PD (the Plastic Stent group), including 25 patients who ultimately underwent metal stent placement. A total of 170 (63%) patients had either a plastic or a metal stent in place at the time of PD (the Any Biliary Stent group), and 92 (34%) patients had had no biliary decompression before PD (the No Biliary Drainage group) (Fig. 1).

Demographics, tumor histology, treatments, and operative characteristics of patients, compared as the Metal Stent group and all other patients, are shown in Table 1. Patients in the Metal Stent group were older (median age, 65 versus 59 years, $P = 0.009$), more likely to have had a histologic diagnosis of adenocarcinoma (86% versus 67%, $P = 0.019$), more likely to have undergone a concomitant vascular resection at the time of PD (38% versus 18%,

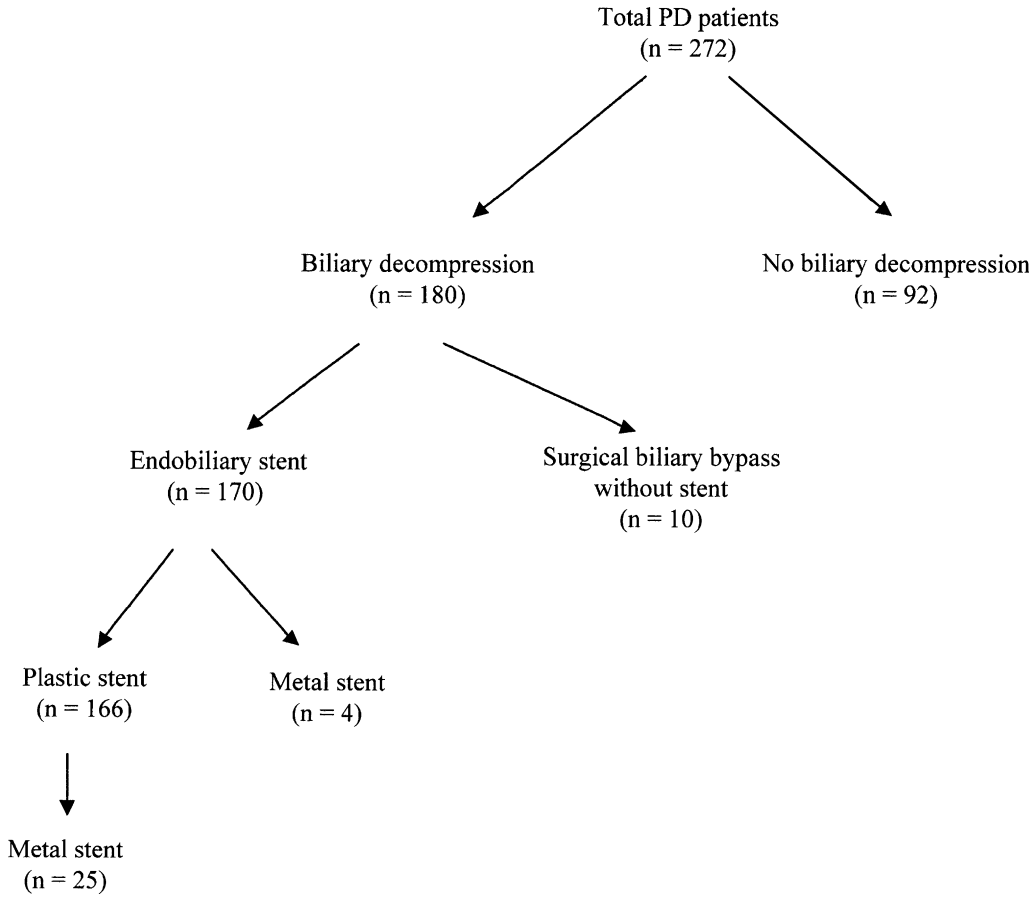

Fig. 1. Flow diagram summarizing the sequence and method of biliary decompression in all 272 patients who underwent pancreaticoduodenectomy. Metal stents were placed in response to occlusion of a plastic stent in 25 patients.

Table 1. Demographics, tumor histology, treatments, and operative characteristics in 272 patients who underwent pancreaticoduodenectomy

Variable	No. of patients (%)			
	Total (n = 272)	Metal Stent (n = 29)	No Metal Stent (n = 243)	Metal Stent vs. No Metal Stent, *P* value*
Demographic factors				
Gender distribution (males/females)	164:108	14:15	150:93	.016
Median age (yr) (range)	59 (22–87)	65 (44–83)	59 (22–87)	.009
Tumor histology and location				
Adenocarcinoma	188 (69)	25 (86)	163 (67)	.019
Pancreas	122 (45)	18 (62)	105 (43)	
Ampulla	40 (15)	6 (21)	34 (14)	
Bile duct	11 (4)	0	11 (5)	
Duodenum	9 (3)	1 (3)	8 (3)	
Other	6 (2)	0	5 (2)	
Other	84 (31)	4 (14)	80 (33)	
Neuroendocrine carcinoma	24 (9)	1 (3)	23 (9)	
Intraductal papillary mucinous neoplasm	13 (5)	1 (3)	12 (5)	
Other malignant tumor	9 (3)	0	9 (4)	
Benign	38 (14)	2 (7)	36 (15)	
Treatment				
Vascular resection	56 (21)	11 (38)	45 (18)	.015
Adjuvant therapy	153 (56)	23 (79)	130 (53)	
Preoperative	115 (42)	22 (76)	93 (38)	<.001
Chemoradiation	105 (38)	18 (62)	87 (36)	
Chemotherapy alone	8 (3)	3 (10)	5 (2)	
Radiation alone	2 (1)	1 (3)	1 (1)	
None	157 (58)	7 (24)	150 (62)	
Postoperative	38 (14)	1 (3)	37 (15)	
Operative characteristics				
Median estimated blood loss (mL) (range)	650 (100–7330)	700 (100–3000)	600 (100–7330)	.88
Median operative time (min) (range)	439 (136–900)	393 (233–774)	400 (136–900)	.97
Median length of hospital stay (days) (range)	10 (4–91)	11 (6–20)	10 (4–91)	.22

*Rows without *P* values had $P > 0.05$.

$P = 0.015$), and much more likely to have received preoperative (neoadjuvant) therapy (76% versus 38%, $P < 0.001$) than all other patients. No significant differences were found between these two groups in operative characteristics, including estimated blood loss and operative time, or in the length of hospital stay.

Perioperative Complications

Major and minor complications observed after PD are listed in Tables 2 and 3. The perioperative mortality rate for all 272 patients was 1.1%, with no deaths in the Metal Stent group and three deaths in the No Metal Stent group (two deaths were in the No Biliary Drainage group). No differences were found in the rates of hospital readmission in the Metal Stent group versus the No Metal Stent group. One or more perioperative complications occurred in 174 (64%) patients, including 20 (69%) patients in the Metal Stent group and 154 (63%) patients in the No Metal Stent group. No differences in the incidence of major or minor complications were found between the two groups, including the rates of pancreatic fistula (7% in the Metal Stent group versus 4% in the No Metal Stent group, $P = 0.41$), intra-abdominal abscess (3% Metal versus 4% No Metal, $P = 0.95$), or wound infection (7% Metal versus 5% No Metal, $P = 0.73$).

Comparisons of readmissions, deaths, and complications after PD between patients who had had any form of biliary stent placed (Any Biliary Stent

Table 2. Perioperative mortality and major and minor complications (Metal Stent versus No Metal Stent Group)

Variable	No. of patients (%)			Metal Stent vs. No Metal Stent, *P* value
	Total (n = 272)	Metal Stent (n = 29)	No Metal Stent (n = 243)	
Perioperative death	3 (1)	0	3 (1)	.55
Readmission	27 (10)	4 (14)	23 (9)	.46
Any complication	174 (64)	20 (69)	154 (63)	
Major complications*	90 (33)	10 (34)	80 (33)	.87
Reoperation	4 (1)	0	4 (2)	.49
Anastomotic leak				
Pancreaticojejunal	11 (4)	2 (7)	9 (4)	.41
Other	2 (1)	0	2 (1)	
Intra-abdominal fluid collection				
Sterile	12 (4)	0	12 (5)	
Abscess	10 (4)	1 (3)	9 (4)	.95
Myocardial infarction	2 (1)	0	2 (1)	
Arrhythmia	14 (5)	3 (10)	11 (4.5)	
Pulmonary	22 (8)	2 (7)	20 (8)	
Gastrointestinal bleeding	12 (4)	2 (7)	10 (4)	
Sepsis syndrome	6 (2)	0	6 (3)	
Minor complications*	84 (31)	10 (34)	74 (30)	
Wound infection	15 (6)	2 (7)	13 (5)	.73
Delayed gastric emptying	26 (10)	1 (3)	25 (10)	
Deep vein thrombosis	3 (1)	0	3 (1)	
Other†	40 (15)	7 (25)	33 (14)	

*Some patients had more than one complication.
†Other includes central venous catheter infection, allergic reaction, drain complication, colitis, urinary tract infection, and chyle leak.

group) and those who had not undergone biliary decompression (No Biliary Drainage group) are shown in Table 3. No differences were found in hospital readmission rates or in postoperative mortality rates between the two groups. Further, no differences were found in the rates of pancreatic fistula (4% in the Any Biliary Stent group versus 5% in the No Biliary Drainage group, $P = 0.46$), intra-abdominal abscess (2% Any Stent versus 6% No Drainage, $P = 0.11$), or wound infection (6% Any Stent versus 4% No Drainage, $P = 0.48$) between the two groups.

Stent Patency, Stent-Related Complications, and Economic Analysis

Findings on the duration of stent patency and stent-related complications are summarized in Table 4. The median duration of stent patency was significantly longer for expandable metal stents compared with plastic stents (125 days versus 43 days, $P < 0.001$) (Fig. 2). The median preoperative interval (defined as the time from initial stent placement to PD) was similar in both the metal stent and the plastic stent groups.

Stent-related complications occurred in only 2 (7%) of the 29 patients with metal stents. One metal stent occlusion, which occurred at 16 months post-insertion, was managed by using a balloon to clear the stent of debris and stones and by placing another metal stent. The other metal stent occlusion, which occurred at 3 months post-insertion, was managed by placing a plastic stent through the existing metal stent. Of the 166 patients with plastic stents, 75 (45%) patients experienced a total of 116 complications, including stent occlusion (98 cases), stent migration (16 cases), and bile duct perforation and hemobilia (1 case each). A total of 113 stent changes were performed in these 166 patients. Forty-five inpatient hospitalizations at M. D. Anderson Cancer Center were required for the management of plastic stent-related complications, most commonly cholangitis. The median length of hospital stay for the management of plastic stent-related complications was 3 days, for a total of 118 hospital days at M. D. Anderson Cancer Center. In this analysis, we excluded all inpatient hospital stays at other medical centers for the treatment of stent-related complications because we did not have access to the medical records at those centers. There were no stent-related deaths.

Table 3. Perioperative mortality and major and minor complications (Any Biliary Stent Group versus No Biliary Drainage Group)

Variable	No. of patients (%)		*P* value
	Any Biliary Stent (n = 170)	No Biliary Drainage (n = 92)	
Perioperative death	1 (1)	2 (2)	.25
Readmission	17 (10)	9 (10)	.46
Major complications*	50 (29)	38 (37)	.05
Reoperation	1 (1)	3 (3)	.15
Anastomotic leak			
Pancreaticojejunal	6 (4)	5 (5)	.46
Other	2 (1)	0	
Intra-abdominal fluid collection			
Sterile	8 (5)	4 (4)	
Abscess	4 (2)	6 (6)	.11
Myocardial infarction	1 (1)	1 (1)	
Arrhythmia	9 (5)	5 (5)	
Pulmonary	12 (7)	9 (10)	
Gastrointestinal bleeding	6 (4)	5 (5)	
Sepsis syndrome	2 (1)	4 (4)	
Minor complications*	50 (29)	31 (30)	
Wound infection	11 (6)	4 (4)	.48
Delayed gastric emptying	13 (3)	10 (9)	
Deep vein thrombosis	1 (1)	2 (2)	
Other†	25 (15)	15 (15)	

*Some patients had more than one complication.
†Includes central venous catheter infection, allergic reaction, drain complication, colitis, urinary tract infection, and chyle leak.

Table 4. Stent patency and stent-related complications

Variable	Metal Stent (n = 29)	Plastic Stent (n = 166)	*P* Value
Duration of patency*			
Median, days	125	43	<.001
Range, days	21–477	2–399	.07
Median preoperative interval, months	4.1	3.9	
Complications			
No. of patients (%)	2 (7)	75 (45)	<.001
Total number of complications (%)†	2 (7)	116 (70)	<.001
Occlusion	2	98	
Migration	0	16	
Perforation of bile duct	0	1	
Hemobilia	0	1	
Stent changes/additions			
Total No.	2	113	<.001
Clinical presentation			
Cholangitis	2 (100)	45 (40)	
Jaundice	0	29 (26)	
Abnormal LFTs	0	15 (13)	
Elective	0	15 (13)	
Unknown	0	8 (7)	
Bile duct perforation	0	1 (1)	
No. of stent changes per patient			
1	2	48	
2	0	21	
3	0	4	
⩾4 (range, 4–7)	0	2	
Inpatient hospitalizations			
No. at M. D. Anderson (%)	1 (3)	45 (27)	<.001
Median length of stay (days) (range)	4 (4)	3 (1–7)	
Total no. of M. D. Anderson hospital days	4	118	

LFTs = liver function tests.
*Duration measured as time either to a complication requiring stent change or to pancreaticoduodenectomy.
†Some patients had more than one stent-related complication.

The economic impact of providing biliary decompression during the preoperative interval is detailed in Table 5. Although the initial expense of placing an endobiliary covered metal stent exceeded that of a plastic stent by $2100, the long-term expenses related to plastic stent-related complications easily eclipsed this amount. The assumptions made in this analysis included a 7% incidence of metal stent-related complications and a 45% incidence of plastic stent-related complications requiring stent exchange; inpatient hospitalization for a median of 3 days for 60% of patients with plastic stent-related complications; and a median preoperative interval of approximately 4 months.

DISCUSSION

Our experience suggests that PD can be performed safely when a metal stent has been placed in the extrahepatic bile duct and that the presence of an endobiliary stent of any kind, metal or plastic, does not increase PD-associated morbidity or mortality. During a median preoperative interval of nearly 4 months, we documented a high rate of complications related to plastic stents, which were associated with significant health care costs and patient morbidity. Thus, we currently favor the placement

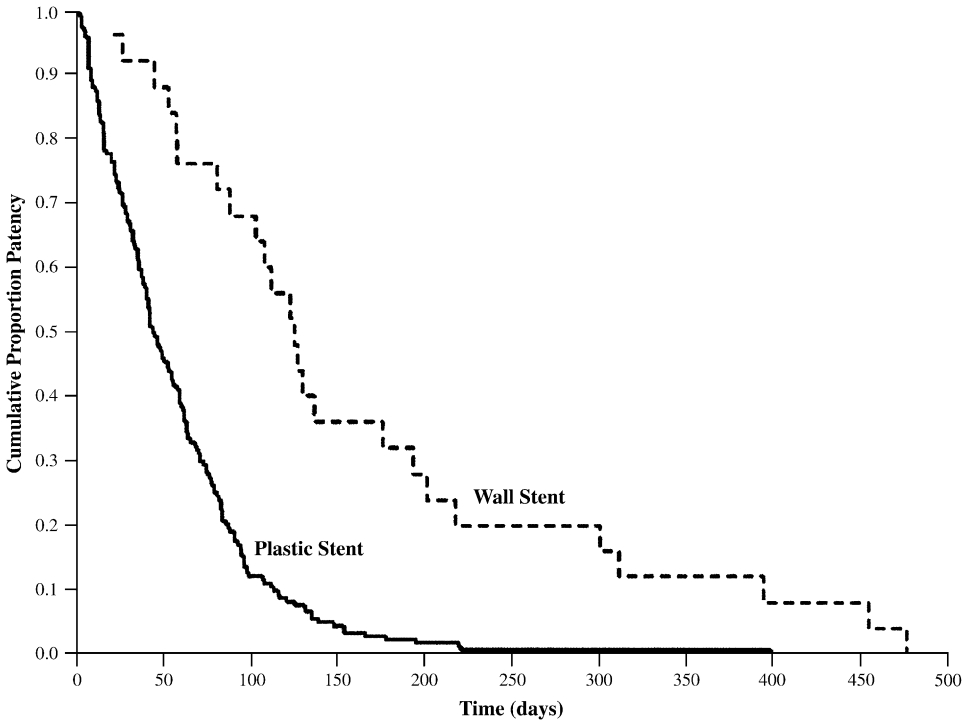

Fig. 2. Actuarial curves for cumulative stent patency as a function of time. Stent patency was defined as the time to occlusion or pancreaticoduodenectomy. Stent patency was significantly longer in the Metal Stent group than in the Plastic Stent group ($P < 0.001$).

of expandable metal stents in patients with symptomatic malignant distal bile duct obstruction for whom surgery is not planned, such as those patients with locally advanced or metastatic disease, or in whom a significant delay in the time to surgery is anticipated, such as in those patients receiving preoperative therapy.

PD was safely performed in all 29 patients who had had an indwelling endobiliary metal stent. Despite the fact that the patients in the Metal Stent group were older, more likely to have undergone concomitant vascular resection with the PD, and much more likely to have received preoperative therapy, the median estimated blood loss and operative time were no different for these patients than for all other patients who underwent PD without a metal stent (including patients who had not had biliary decompression). At the time of surgery, the metal stent was either separately removed from the bile duct or was left in situ and removed together with the resected specimen.

Although previous reports have suggested that preoperative biliary drainage increases PD-associated morbidity[1–3] and mortality,[1] including a report from our own institution showing higher rates of wound infections in patients who had had biliary stents,[4] we did not find this to be the case. In fact, we found no difference in the incidence of perioperative death or morbidity, including the rates of pancreatic fistula, intra-abdominal abscess, and wound infection, in patients treated with a metal stent, a plastic stent, or no biliary drainage. The difference in superficial wound infection rates between the previous study[4] and this one may relate to differences in attentiveness to wound irrigation and closure; however, the extent to which this may have influenced the current results cannot be quantified. The rate of pancreatic fistula also was low in the current series, perhaps because we no longer routinely place intra-abdominal drains adjacent to the pancreaticojejunal anastomosis, leaving subclinical pancreatic leaks undetected.

Our study provides further evidence that extrahepatic biliary obstruction can be safely managed with nonsurgical (endoscopic) biliary decompression to permit timely palliation of symptoms and careful treatment planning. CT scans should always be obtained before endoscopic biliary stent placement to avoid imaging artifact related to the stent itself as well as confusion regarding the extent of disease in the event of procedure-related pancreatitis.

Our findings also suggest that most patients who present with symptomatic distal bile duct obstruction secondary to pancreatic cancer can be best treated with an expandable endobiliary metal stent at

Table 5. Economic impact of maintaining biliary decompression during the preoperative interval

Procedures	Charges (in U.S. $)	
	Per Patient	Per 100 patients
Covered metal stent	2,170	217,000
Plastic stent	75	7,500
Additional expense of a metal stent	2,100	*209,500*
Stent repair or exchange for occlusion		
ERCP with stent exchange	3,100	
Anesthesia for 1 hour	680	
Recovery room for 1.5 hours	550	
Emergency department visit × 60%*	270	
Hospital bed for 3 days × 60%*	2,000	
Intravenous fluids and medications for 3 days × 60%*	900	
Additional expense of a stent occlusion	7,500	
Frequency of stent occlusion		
Metal: 7%		52,500
Plastic: 45%		337,500
Additional expense of plastic stent exchanges		*285,000*

ERCP = endoscopic retrograde cholangiopancreatography.
*The assumption is that 60% of patients with a stent occlusion will require inpatient hospitalization for a median 3 days.

their first (and hopefully last) biliary drainage procedure (Fig. 3). Approximately 50% of patients diagnosed with pancreatic cancer have evidence of metastatic (stage IV) disease at presentation and with systemic therapy the median survival time for such patients is approximately 5–6 months.[17] Excluding those patients with extensive tumor burden and poor performance status, for whom plastic stent placement and hospice care seem a reasonable approach, we recommend that an endobiliary metal stent be placed in other patients with metastatic disease who are expected to live longer than 2 months and thus would potentially require one or more exchanges of a plastic stent. An additional 30–35% of patients with pancreatic cancer will present with locally advanced (stage III) disease that cannot be resected; such patients have a median survival time of 10–12 months with local and systemic therapies.[18] Given this anticipated life expectancy, patients with stage III disease and symptomatic jaundice should also undergo metal stent placement. Indeed, several randomized trials have demonstrated the superiority of metal stents over plastic ones in terms of patency and cost-effectiveness for patients with inoperable malignant strictures of the common bile duct who are expected to live more than 5 or 6 months.[10,11,19] Our findings here confirm the brief period of patency seen with plastic stents and dispel the myth that a metal prosthesis within the bile duct complicates subsequent PD.

On the basis of this preliminary experience, we recommend placement of metal stents for patients with symptomatic jaundice and clearly resectable periampullary malignancies if a delay of more than 6 weeks is anticipated before surgery, as would be expected with most contemporary preoperative chemoradiation treatment regimens. Moreover, we recommend placement of a *covered* metal stent whenever possible to minimize the risk of tumor ingrowth into the interstices of the stent as well as to facilitate its removal at the time of PD. This practice is based in part on results of a prospective study which randomized 112 patients to either a covered metal stent (n = 57) or an uncovered metal stent (n = 55) for the management of malignant distal bile duct obstruction; covered stents had a significantly greater cumulative stent patency (related to an absence of tumor ingrowth) compared with the uncovered stents.[20] However, there were two episodes of acute cholecystitis in the covered stent group due to overlap of the cystic duct orifice by the covered portion of the stent, compared with no episodes of acute cholecystitis in the uncovered metal stent group. Thus, we situate the superior-most portion of the stent below the insertion of the cystic duct into the common hepatic duct in order to permit continued drainage of bile from the gallbladder via the cystic duct, thus avoiding the potential complication of cholecystitis. In the few patients in whom the cystic duct inserts more inferiorly into the common hepatic duct, an *uncovered* metal stent is placed to obviate this complication.

Importantly, there are some patients with symptomatic distal bile duct obstruction who should *not* undergo endobiliary metal stent placement. Patients for whom the diagnosis is problematic, such as those without an obvious mass in the head of the pancreas or with a history of pancreatitis, should have a plastic stent placed at the first endoscopic intervention to permit easy removal of the stent and additional diagnostic studies as needed. Although covered metal stents can be removed endoscopically,[21] they should not be used to provide short-term biliary decompression; when the preoperative interval is less than 6 weeks, plastic stent dysfunction is uncommon and thus plastic stent placement is more cost-effective.[9] Therefore, patients who require endobiliary decompression for only a few weeks before PD, such as

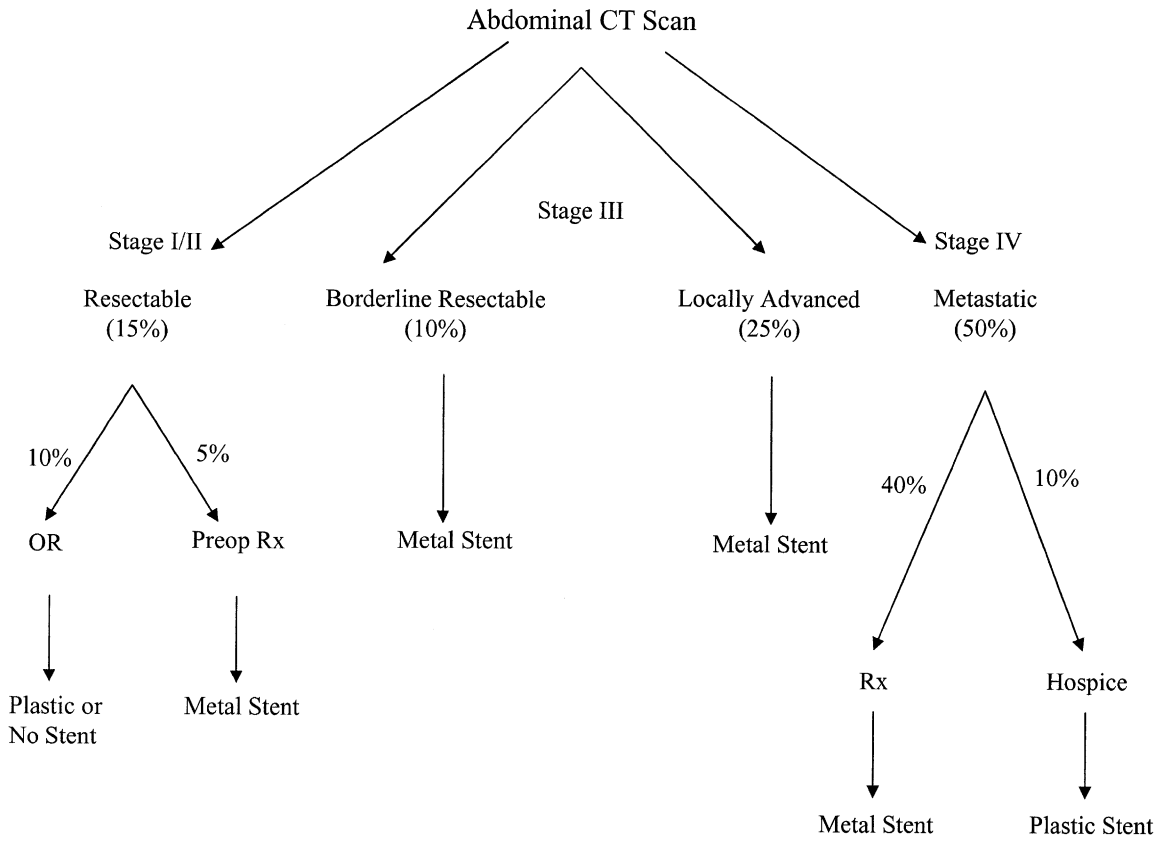

Fig. 3. Algorithm for the placement of endobiliary metal or plastic stents according to the extent of disease on pretreatment abdominal computed tomography scanning. Numbers in parentheses represent estimated percentages for the number of patients in each clinical stage. Assuming that 10% of all patients with symptomatic malignant distal bile duct obstruction proceed directly to the operating room (OR) and another 10% of patients choose hospice care, 80% of all patients are candidates for metal stent placement at the time of the initial endoscopic intervention. Rx = treatment (systemic chemotherapy).

those with hepatic or hematologic complications from prolonged jaundice or those who require other detailed medical evaluation to optimize their preparation for major surgery, should also undergo plastic stent placement.

We acknowledge several limitations of this study, including the small number of patients in the Metal Stent group, the retrospective design of the study (especially with respect to the detection of complications), and the absence of a control group that underwent metal stent placement but did not undergo successful PD. The latter group is of potential significance, as metal endobiliary stents should not be placed if the presence of the stent itself within the bile duct precludes subsequent PD. In an effort to answer this question, we audited our current preoperative clinical trial (protocol ID 01-341) and found that only 1 of the 77 patients treated on this protocol to date had locally unresectable disease secondary to extensive portal inflammation that might have been related to the indwelling metal stent. Moreover, it is unlikely that the metal stent itself was responsible for the higher rate of vascular resections in the Metal Stent group in the current study, as the common bile duct is in a more posterior plane than is the superior mesenteric-portal vein confluence, which is the most common site of vascular involvement by tumor that would mandate vascular resection. The need for concomitant vascular resection in the Metal Stent group is likely related to the fact that these patients were much more likely to receive a prolonged course of neoadjuvant therapy, presumably as treatment for large, borderline-resectable tumors with mesenteric venous involvement.

In summary, our initial experience with PD in patients with indwelling metal endobiliary stents indicates that this practice was not associated with an increase in operative or perioperative complications related to the metal stent. Our results also indicate that regardless of the type of stent used, preoperative

biliary decompression can be done without increasing perioperative mortality or morbidity over that associated with no biliary decompression at all. Finally, our findings suggest that the vast majority of patients with symptomatic malignant distal bile duct obstruction may be best served by placement of a metal stent rather than a plastic stent at the initial endoscopic intervention. This approach minimizes complications and appears to be the most cost-effective treatment schema even if the stage of disease and treatment plan are not completely defined at that time.

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Discussion

Dr. M. Callery (Boston, MA): Your fine presentation dispels the myth that metal stents can create peril for the operating surgeon during Whipple procedure for pancreatic cancer, and you have avoided, I hope, creating a new myth that metal endobiliary stents are preferable initially in resectable disease. After all, it was your unacceptable stent occlusion rates over 4 months of preoperative therapy that forced your hands to these metal stents, and that is fine. I have three brief questions for you.

First, could you tell us whether the metal stents may have contributed to your unsuccessful resection attempts, because that is really the issue here, not how well you did with your successful resections?

Second, when, if ever, do you advocate using plastic stents at M. D. Anderson?

And then finally, could you summarize, going from your last slide, the order and timing of your diagnostic tests and treatments for the jaundiced patient presenting with a localized pancreatic head mass?

Dr. Mullen: Thank you for those excellent questions. I will start with your last question first. For the patient referred to M. D. Anderson with a confirmed or a presumed diagnosis of pancreatic cancer, we first obtain laboratory studies including serum creatinine. If this value is acceptable, we then obtain a pancreas protocol abdominal CT scan, consisting of image acquisition during both the arterial and venous phases of contrast administration as well as thin (1.25–2.5 mm) cuts through the pancreas. The radiologist and the surgeon together review the CT scan and on this basis define the stage of disease as either resectable, borderline resectable, locally advanced, or metastatic. The patient then sees Dr. Evans or one of the other pancreatic surgeons in the clinic and a treatment plan is formulated.

An appointment is made with the GI endoscopy team well in advance of the patient's arrival to M. D. Anderson should it be necessary to obtain a tissue diagnosis (such as for preoperative therapy) and/or to place or exchange an existing endobiliary stent for biliary decompression. Note that many patients referred to our center have already undergone prereferral endobiliary plastic stent placement. If a tissue diagnosis is needed, an endoscopic ultrasound with FNA is performed at that time.

For the patient with biopsy-proven pancreatic cancer who is to be enrolled in our preoperative chemoradiation protocol, the plastic stent is exchanged for an expandable, covered metal stent. If a diagnosis cannot be obtained by EUS-FNA, then the plastic stent is removed, brushings are obtained from the bile duct, and if the diagnosis is established in that setting with immediate cytopathology, then an expandable metal stent is inserted into the bile duct. If the diagnosis is in doubt or if additional studies are planned, then a temporary plastic stent is placed.

To answer your previous question, has the metal stent itself precluded resection in any patient, we have in fact recently audited our protocol study population. So far there are 77 patients on this gemcitabine-based chemoradiation protocol, and in looking back at the operative reports, we identified three patients who were locally unresectable at the time of surgery. Two of these three patients had metal stents in place. The operative report describes a difficult portal dissection in one patient that was perhaps related to local inflammation secondary to the metal stent. So perhaps in 1 of 77 patients the metal stent precluded resection.

Your third question, pertaining to our indications for plastic stent placement, is an important one. This study consists of a select group of patients, many of whom are enrolled in a lengthy preoperative treatment regimen, and so there is a significant delay to surgery. Certainly, for the patient with biliary obstruction who is not interested in a course of preoperative therapy or for whom you anticipate a timely operation, a plastic stent is a very reasonable choice. In addition, for the patient who has a high burden of metastatic disease such that their life expectancy is less than 2–3 months, it is more cost-effective to place a plastic stent.

Importantly, we recommend plastic stent placement in patients who represent a diagnostic dilemma. If you are uncertain of the diagnosis, such as in the case of the patient without an obvious mass in the head of the pancreas on CT scan imaging, such that you might even be considering benign diagnoses such as autoimmune or chronic pancreatitis, we recommend plastic stent placement in this group of patients as well.

Effects of Gastric Bypass Procedures on Bone Mineral Density, Calcium, Parathyroid Hormone, and Vitamin D

Jason M. Johnson, D.O., James W. Maher, M.D., Isaac Samuel, M.D., Deborah Heitshusen, R.N., Cornelius Doherty, M.D., Robert W. Downs, M.D.

Weight loss after gastric bypass procedures has been well studied, but the long-term metabolic sequelae are not known. Data on bone mineral density (BMD), calcium, parathyroid hormone, and vitamin D were collected preoperatively and at yearly intervals after gastric bypass procedures. A total of 230 patients underwent preoperative BMD scans. Fifteen patients were osteopenic preoperatively, and three patients subsequently developed osteopenia postoperatively within the first year. No patient had or developed osteoporosis. At 1 year, total forearm BMD decreased by 0.55% (n = 91; $P = .03$) and radius BMD had increased overall by 1.85% (n = 23; $P = .008$); both total hip and lumbar spine BMD decreased by 9.27% (n = 22; $P < .001$) and 4.53% (n = 31; $P < .001$), respectively. By the second postoperative year, BMD in the total forearm had decreased an additional 3.62% (n = 14; $P < .001$), whereas radius BMD remained unchanged. Although total hip and lumbar spine BMD significantly decreased at 1 year, by year 2 both total hip and lumbar spine BMD only slightly decreased and were not significantly different from before the operation. Serum calcium decreased from 9.8 mg/dL to 9.2 during the first year (not significant [NS]) and then to 8.8 (NS) by the second year. Parathyroid hormone increased from 59.7 pg/mL (nl 10–65 pg/mL) preoperatively to 63.1 during year 1 (NS) and continued to increase to 64.7 by year 2 (NS). No difference was noted among levels of 25-hydroxy vitamin D preoperatively (25.2 ng/mL; nl 10–65 ng/mL), at 1 year (34.4), and at 2 years (35.4). Our data indicate that bone loss is highest in the first year after gastric bypass with stabilization, and that, in some cases, there is an increase in bone density after the first year. (J GASTROINTEST SURG 2005;9:1106–1111) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Gastric bypass, bone mineral density, morbid obesity, surgery

Morbid obesity is an epidemic in the United States.[1] From 1976 to 2000 the rate of obesity in this country doubled, from 15% to more than 30%.[2] The economic impact of obesity to society, and in particular obesity-related diseases, is significant. Health care expenditures for morbidly obese patients can be twice as much as for those of healthy weight.[3]

Behavioral and medical weight-loss programs have been unsuccessful at producing enough weight loss to realize improvements in comorbid conditions.[4] As such, gastric bypass procedures have become the mainstay for treatment of severe obesity, and it has been well documented that gastric bypass produces a significant durable weight loss and ameliorates or cures many comorbid conditions.[5,6] It has long been recognized that gastric bypass might have effects on calcium metabolism and bone density, but the long-term endocrine side effects of the operation remain poorly elucidated. This is a prospective study of the effects of gastric bypass on bone mineral density (BMD), calcium, and parathyroid hormone (PTH) levels.

METHODS

An analysis of 233 patients undergoing either gastric bypass (laparoscopic or open) or biliopancreatic diversion at the University of Iowa between March 2000 and November 2004 was performed. All patients met the National Institutes of Health criteria

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for morbid obesity surgery (body mass index > 40 kg/m^2 or body mass index > 35 kg/m^2 with comorbid conditions). A total of 230 patients underwent preoperative BMD scanning. At the beginning of the data-collection routine, preoperative calcium, PTH, and 25-hydroxy vitamin D levels were not noted, but this became routine preoperatively and at annual laboratory testing as the series progressed.

The prospective collection of data in our bariatric database was approved by the institutional review board at the University of Iowa Medical Center, and all patients consented to be enrolled in the data-collection process.

Statistical Analysis

The Student *t* test was used to determine the significance of percent decrease (or increase) in BMD from preoperative BMD scans and at yearly intervals to 4 years postoperatively. Changes in mean serum calcium, PTH, and 25-hydroxy vitamin D were analyzed with analysis of variance and Dunnett's post-test to determine whether significant changes occurred from preoperative levels compared with postoperative levels. *P* values less than .05 were considered statistically significant.

RESULTS

During the study period seven biliopancreatic diversions and 226 gastric bypasses were performed. Of the gastric bypasses performed, 82% (n = 192) were performed laparoscopically. The conversion rate for the laparoscopic cases was 8.1%. The average preoperative body mass index was 50.5 kg/m^2 for the group as a whole (49.6 kg/m^2 for women [n = 187] and 54.4 kg/m^2 for men [n = 46]). The average age was 38.6 years for women and 43.4 years for men. At the beginning of the gastric bypass experience all patients were administered 500 mg of oral calcium (Tums) and a multivitamin three times per day.

BMD scans of the total forearm (TF), radius bone (RB), total hip (TH), and/or lumbar spine (LS) were performed preoperatively on 230 patients. Most of the patients who underwent preoperative BMD scans had TF or RB measured because of the weight limitations in obtaining LS and hip BMD measurements. Fifteen patients had osteopenia preoperatively, and three patients subsequently developed osteopenia within the first year postoperatively as determined by their BMD scans. No patients had or developed osteoporosis during follow-up, as demonstrated by their BMD scans. At 1 year, BMD values for TF decreased by 0.55% (n = 91; $P = .03$) and RB increased by 1.85% (n = 23; $P = .008$). TH and LS bone density decreased by 9.27% (n = 22; $P < .001$) and 4.53% (n = 21; $P < .001$), respectively, during the first postoperative year. During the second postoperative year, TF bone density continued to decrease an additional 3.62% (n = 14; $P < .001$), whereas RB, TH, and LS bone density stabilized. The number of patients eligible for 3-year follow-up is small (n = 23) (Table 1, Fig. 1). After the initial decrease in BMD the first 1 to 2 years after surgery, bone density seemed to stabilize with no further decreases, but it did not start to increase to the preoperative levels. Each patient was used as his or her own control, and the results were compared with the previous BMD scans.

Mean serum calcium decreased from 9.8 mg/dL (nl 8.4–10.2 mg/dL) to 9.2 mg/dL (not significant [NS]) during the first postoperative year and then to 8.8 mg/dL by year 2 (NS). Conversely, PTH levels increased from a preoperative level of 59.7 pg/mL (nl 10–65 pg/mL) to 63.1 pg/mL at year 1 (NS) and then up to 64.7 pg/mL by year 2 (NS). No difference was noted between 25-hydroxy vitamin D levels preoperatively (25.3 ng/mL [quoted laboratory normal: 10–65 ng/mL]), at 1 year (34.4 ng/mL), and at 2 years (35.4 ng/mL).

Fifty patients demonstrated preoperative evidence of elevated PTH values (>65 pg/mL). Of the patients with a preoperative elevated PTH level, all had normal calcium levels, and only one had a low 25-hydroxy vitamin D level. Although the mean PTH level at 1 and 2 years was within normal levels, 37 patients at year 1 and 18 patients at year 2 had elevated PTH levels, of which only one individual had a low 25-hydroxy vitamin D level. Preoperative vitamin D levels were between 20 and 30 ng/mL in 17 patients, 10 and 20 ng/mL in 20 patients, and less than 10 ng/mL in four patients. Despite elevations in PTH levels, serum calcium remained consistent with only one person exhibiting hypocalcemia (<8.2 mg/dL). Hypercalcemia did not develop in any patients throughout the study period.

DISCUSSION

As obesity continues to increase in the United States, the demand for obesity surgery will increase. The endocrine side effects of gastric bypass procedures are poorly studied. As the age of patients seeking morbid obesity surgery continues to decrease, the long-term clinical significance of endocrine derangements, especially bone turnover, becomes of utmost importance.

Metabolic bone disease, hypocalcemia, hyperparathyroidism, and osteoporosis have been well

Table 1. Bone mineral density values from different areas to 3 years postoperatively

	Year 1			Year 2			Year 3		
	% Decrease	n	*P*	% Decrease	n	*P*	% Decrease	n	*P*
Total forearm (TF)	−0.55% ± 2.43%	91	.03	−3.62% ± 3.56%	31	<.001	−1.83% ± 2.42%	9	NS
Radius bone (RB)	1.85% ± 4.06%	23	.008	0.06% ± 3.06%	14	NS	−1.03% ± 2.23%	8	NS
Total hip (TH)	−9.27% ± 3.42%	22	<.001	−1.35% ± 3.24%	6	NS	−0.73% ± 3.76%	3	NS
Lumbar spine	−4.53% ± 3.83%	14	<.001	−0.32% ± 2.42%	6	NS	0.53% ± 2.15%	3	NS

described after gastric surgery, but the effects of Roux-en-Y gastric bypass (RYGB) for obesity on these same parameters are not as defined.[7] Recently, more research has been performed to understand the effects of gastric bypass operations on bone turnover and density. Several authors have shown that both serum osteocalcin and urinary n-telopeptide, markers of bone turnover, are elevated in the first year after surgery in patients who undergo RYGB when compared with control groups.[8,9] In addition, several small studies with short follow-ups have suggested that BMD decreases after gastric bypass procedures.[8,10]

It is known that the majority of calcium is absorbed in the duodenum and proximal jejunum, so bypassing this portion of the intestines might naturally predispose individuals to hypocalcemia.[11,12] In addition, vitamin D is also needed for the intestinal absorption of calcium. By creating a Roux anastomosis, there is poor mixing of bile salts with fat, which results in impaired fat absorption and ultimately may produce malabsorption of vitamin D.[13,14] The failure of the bile salts to mix appropriately may then cause increased intraluminal fat and steatorrhea, which may further decrease calcium absorption.[13,15]

Crowley and colleagues[16] demonstrated that after gastric bypass surgery, and without oral supplementation, the majority of patients ingest less than half of the recommended daily vitamin D and approximately 50% of the daily recommended calcium. Although the observed decrease in calcium and slight increase in 25-hydroxy vitamin D were not statistically significant, our data do indicate that despite supplementation with oral calcium there is a need for additional

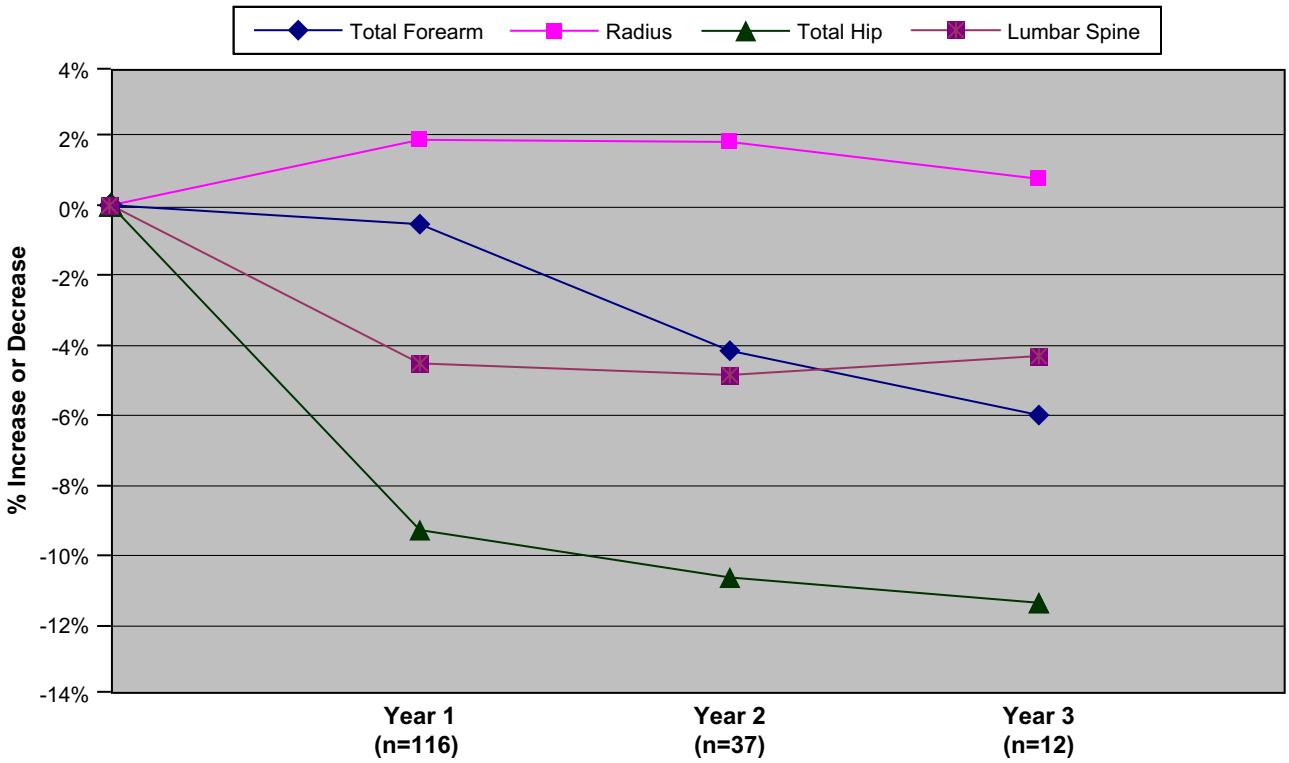

Fig. 1. BMD to 3 years Post-Op

vitamin D supplementation. Ongoing laboratory analysis is required to determine whether adequate supplementation is being consumed.

PTH serves to increase production of 1,25-dihydroxy vitamin D and increase reabsorption of calcium from the bone.[12] In addition, deficiencies of vitamin D result in an elevation in PTH. The decision to use PTH, as opposed to bone-specific alkaline phosphatase, was made because PTH levels are directly influenced by vitamin D, whereas alkaline phosphatase is indirectly affected by vitamin D.[17] Our study supports previously described data that obesity may predispose one to abnormalities in PTH, as can be seen by the fact that 50 patients had elevated PTH levels preoperatively with normal calcium and laboratory-quoted normal 25-hydroxy vitamin D levels.[18] However, the significance of the elevations of PTH without other abnormalities remains to be elucidated. It is becoming more accepted that by the time a person's 25-hydroxy vitamin D levels reach 10 ng/mL (the quoted low normal for most laboratories), he or she is already profoundly deficient in vitamin D.[19,20] As a result, most endocrinologists are advocating maintaining vitamin D levels greater than 25 to 30 ng/mL to prevent the sequelae of deficiencies in vitamin D. Our data demonstrate that 41 patients had preoperative 25-hydroxy vitamin D levels less than 30 ng/mL, which reinforces previous data indicating that obese persons are predisposed to vitamin D deficiencies.[21]

It is known that secondary hyperparathyroidism often precedes osteoporosis and is a direct result of ongoing hypocalcemia and/or vitamin D deficiency.[11] Although the average PTH level of our patients remained below the upper normal levels, the overall trend during the first 2 years postoperatively was toward secondary hyperparathyroidism. The significance of the observed upward trend of PTH is unknown at this point, but it may be an indicator of early vitamin D deficiency. Now that we have instituted an aggressive replacement protocol for vitamin D levels, to maintain a minimum of 30 ng/mL, it is hoped that we will see a downward trend of PTH as we continue to follow these patients.

By using each patient as his or her own control, our data demonstrate that there is a decrease in the BMD for the first year or two after gastric bypass (Fig. 1). This loss in bone density in the first year has been shown by short-term studies, but our data indicate that the bone loss is not an ongoing process, and that after the first year there is no further bone loss.[8] However, no increase in bone density was seen 3 years after gastric bypass. The RB density was the only one of the four locations measured that showed an increase in bone density. The RB, as a site with predominantly cortical bone, may behave differently than the TH and LS, which have greater contribution of cancellous bone. This same increase in RB density only was also noted by Coates and colleagues,[8] who followed BMD in 15 patients for 9 months after gastric bypass surgery.

The clinical significance of the observed decreases in BMD in the TF, TH, and LS has yet to be delineated because of the lack of long-term data regarding bone density. It also remains to be seen whether these decreases will be associated with the pathologic conditions after gastric bypass procedures. It is thought that obesity potentially confers protection from osteoporosis when case-controlled comparisons are made between obese and nonobese patients.[22,23] It is possible that as obese patients lose a significant amount of their excess body weight, which typically occurs in the first year after gastric bypass, that the decrease in BMD seen in our data is simply the loss of the protective effect of obesity on bone density.

Recently, von Mach and associates[10] evaluated BMD and losses in four patients after RYGB compared with nine patients who underwent adjustable silicone gastric banding. Estimated bone area and BMD decreased in all four patients who underwent an RYGB, but both bone area and BMD stayed the same in patients who underwent gastric banding, suggesting that the rerouting of the intestines in RYGB plays the largest role in calcium and vitamin D malabsorption.

To our knowledge this study represents the largest collection of BMD studies performed on patients before and after gastric bypass operations. The importance of adequate calcium and vitamin D supplementation in patients undergoing obesity surgery is apparent from our data. Currently we recommend at least 600 to 1000 mg of calcium per day and an additional 400 to 800 IU of vitamin D per day. We also annually screen each patient's calcium, vitamin D, and PTH levels to detect those who are deficient and aggressively replenish levels in an attempt to prevent metabolic bone disease, osteoporosis, and/or osteomalacia. BMD scanning should be completed in individuals at increased risk of osteopenia and osteoporosis, especially in perimenopausal and postmenopausal women. Further studies are indicated to evaluate the actual effects of gastric bypass operations on bone density over the long-term.

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Discussion

Dr. Michael Sarr (Rochester, MN): That was a great article representing a lot of work. Because most people undergoing bariatric surgery are women, and we know the incidence of metabolic bone disease is higher in women, this is a timely study.

I have a couple of questions. First, I remember that bone mineral density tends to be greater in people with morbid obesity, but I can't quote a specific study. If that is true, what is the clinical significance of the changes that you have shown us? Granted, we can see that the percent of bone mineral density (BMD) decreases, but is that really clinically significant?

Second, alkaline phosphatase is a lot cheaper than measuring parathyroid hormone. Would that be another means of screening patients for increases in bone turnover?

Third, how are you currently following vitamin D status? You are trying to get the serum concentration over 30. Are you giving enough vitamin D with your supplements? How aggressively are you following patients with your recommendations?

Dr. Johnson: First of all, the clinical significance of the initial decrease in BMD is unknown. We really don't know what is going to happen to these people 5 and 6 years down the road. We have shown that bone loss is not an ongoing process; the loss does stabilize. I think that one of the keys here is to follow these patients for 10 and 15 years. The only studies up to now are just snapshots of patients. Until our study the literature didn't have studies in which there were preoperative controls like we have established. So I think the longer we follow these patients, that question will be better answered.

As far as alkaline phosphatase, we have not been checking that, but I think that it may potentially provide some insight as a lower cost test.

Currently we screen everybody for vitamin D deficiency at their annual follow-up, and we do replace accordingly. The problem that we have is ensuring

that patients are actually compliant with their medications. If they come in and are severely vitamin D deficient, are they truly taking their multivitamin and calcium with vitamin D or are they not compliant? The first thing that we want to ensure is that they are truly compliant with their regimen, and then if they are deficient, we will follow that closer.

Dr. Michael Zenilman (Brooklyn, NY): This is a very nice study. I noted that the density curves paralleled the weight loss, but not to the same percent level of loss. To echo Dr. Sarr's comment, is this really clinically significant? What happened in your patients who regained their weight—did the bone density increase back up again?

Dr. Johnson: That we did not look at. I can tell you that since the program was established in 2000, we haven't seen a lot of weight gain because it has only been about 4 years from when the actual program started. We did not look at those who had actually regained weight to see if their bone density increased.

Dr. Zenilman: A second question: Did you compare the bone densities with normal controls? If you did you could tell if their densities are trending to a more normal level after losing weight, which may be the physiologic phenomenon you observed.

Dr. Johnson: I think that may be something to look at in the future.

Dr. Martin Schilling (Hamburg/Saar, Germany): This was a very beautiful study. If you look at your data closely, you find that you had the highest bone density loss in the lower extremity and vertebral spine. Couldn't it just be that the patients losing weight during the first year had less mechanical stress on their lower spine and their bones and for that reason just have less density in the bones?

Dr. Johnson: Yes, as these patients begin to exercise and get on a set routine and undergo weight loss and thus a loss in bone density due to the stress from exercise. However, we are not certain why there was a loss of bone density in those areas and a regaining in the radius.

Dr. Richard Hodin (Boston, MA): I want to bring up a question and an issue about a factor that affects vitamin D levels probably more than diet, and that is sunlight exposure. I wonder if you have had a chance to try to figure out whether patients are changing their amount of sunlight exposure as a function of surgery.

Dr. Johnson: The short answer is no, we didn't, but I think that is a good point.

Is Roux-en-Y Gastric Bypass Surgery the Most Effective Treatment for Type 2 Diabetes Mellitus in Morbidly Obese Patients?

Alfonso Torquati, M.D., M.S.C.I., Rami Lutfi, M.D., Naji Abumrad, M.D., William O. Richards, M.D.

Type 2 diabetes mellitus (T2DM) has a very strong association with obesity. The aim of our study was to analyze the effects of Roux-en-Y gastric bypass (RYGB) surgery on the glucose metabolism in morbidly obese patients with T2DM. Morbidly obese patients (n = 117) with T2DM underwent measurements of fasting serum glucose and glycosylated hemoglobin (HbA1C) at baseline, 6 months, and 12 months after laparoscopic RYGB surgery. Logistic regression was used in both univariate and multivariate modeling to identify independent variables associated with complete resolution of T2DM. Twelve months after surgery, fasting plasma glucose decreased from a preoperative mean of 164 ± 55 mg/dL to 101 ± 38 mg/dL (P = .001) and HbA1C decreased from a preoperative mean of 7.7% ± 1.5% to 6.0% ± 1.1% (P = .001). Resolution of T2DM was achieved in 72 patients (74%). All of the remaining 25 patients decreased the daily medication requirements. On univariate analysis, preoperative variables associated with resolution of T2DM were waist circumference, HbA1C, and absence of insulin treatment. Waist circumference (odds ratio 2.4; 95% confidence interval 1.4–4.1; P = .001) and treatment without insulin (odds ratio 42.2; 95% confidence interval 4.3–417.3; P = .002) remained significant predictors of T2DM resolution in the multivariate logistic regression model after adjusting for covariates. Laparoscopic RYGBP resulted in significant resolution of T2DM. Peripheral fat distribution (smaller waist circumference) and absence of insulin treatment were independent and significant predictors of complete resolution of T2DM. (J GASTROINTEST SURG 2005;9:1112–1118) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Morbid obesity, bariatric surgery, gastric bypass, diabetes, weight loss

Obesity causes an enormous burden for public health. Data from the 2001 Behavioral Risk Factor Surveillance System, a cross-sectional survey conducted by the Centers for Disease Control and state health departments, estimated incidence in obesity at 20.9% among U.S. adults.[1] Type 2 diabetes mellitus (T2DM) is strongly associated with obesity. Approximately 90% of individuals with T2DM are overweight or obese.[1] The lifetime risk of acquiring T2DM is 50% in subjects with morbid obesity, and 63.5% of patients with T2DM have a body mass index (BMI) $\geqslant$ 30 kg/m^2.[1] Diabetes is the leading cause of renal failure, blindness, and amputations, and is a major risk factor for heart disease and stroke.[2,3] An upper body or central distribution of body fat is a major risk factor for T2DM, regardless of the overall degree of obesity.[4] In obese patients with T2DM, weight loss that leads to reduction in visceral fat has been related to improvements in glycemic control, insulin sensitivity, and lipid profile.[5] Short-term studies lasting 12 months or less have demonstrated that weight loss in overweight or obese subjects with T2DM is associated with decreased insulin resistance, substantial improvements in measures of glycemic control, reduced lipemia, and reduced blood pressure.[6–9] However, long-term data substantiating that these improvements can be maintained are limited. Among the various modalities used to treat obesity, Roux-en-Y gastric bypass (RYGB) surgery represents the most effective for sustained weight loss.[10,11] RYGB in obese diabetic patients helps them to become normoglycemic,

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consequently decreasing the risk for vascular diseases, but prospective data regarding resolution of T2DM after RYGB have been scant.[10,11] Therefore, the aim of our study was to analyze the effect of RYGB in a prospective cohort of morbidly obese patients with T2DM and to identify patient factors associated with complete resolution of T2DM.

MATERIAL AND METHODS

Patients

The study, after institutional review board approval, was conducted at Vanderbilt University Medical Center. Morbidly obese patients with T2DM who were undergoing laparoscopic RYGB were enrolled in the study. Eligibility criteria were age 18 to 60 years, diagnosis of T2DM with glycosylated hemoglobin (HbA1C) $\geq$ 6.5%, BMI $\geq$ 35 kg/m^2, stable weight for the previous 3 months, and constant doses of any oral diabetes medications or insulin for at least 1 month. Exclusionary criteria included use of any weight-loss product or participation in any formal weight-loss program in the previous month and diagnosis of type 1 diabetes mellitus. Diagnosis of T2DM was based on fasting plasma glucose concentrations according to criteria established by the American Diabetes Association.[12]

At baseline and each follow-up visit (6 and 12 months) body weight was recorded and blood samples for fasting glucose and HbA1C were obtained. Waist circumference, a surrogate marker of central obesity, was measured by a plastic tape meter at the level of the umbilicus at baseline.

Outcome Measures

The primary outcome measure was resolution of T2DM at 1-year follow-up visit. Complete resolution of T2DM was defined by normal levels of fasting plasma glucose and HbA1C after discontinuing medical treatment. Secondary end points measured included fasting serum glucose and HbA1C at 1-year follow-up visit. Fasting plasma glucose and HbA1C were determined in the Biochemistry Laboratory of Vanderbilt University Medical Center. Plasma glucose was determined by a glucose oxidase method. HbA1C was determined by high-pressure liquid chromatography using a Diamet Glycosylated Hemoglobin Analyzer (Bio-Rad Laboratories, Hercules, CA). One-year excess weight loss (EWL) was also calculated. EWL was defined as the excess weight over the ideal body weight calculated according to the Metropolitan Life Weight Tables (Source: Metropolitan Life Insurance Company).

Surgical Technique

All operations were performed laparoscopically using the same technique. A divided 15 to 20 mL gastric pouch was anastomosed with the roux limb in a retrocolic retrogastric fashion. The length of the roux limb varied according to the preoperative BMI (35–40: 75 cm, 40–50: 100 cm, $>$50: 150 cm).

Statistical Analysis

The data are presented as mean $\pm$ standard deviation for continuous variables, and as counts or proportions (%) for categoric variables. Binary logistic regression analysis was used in both univariate and multivariate modeling to identify independent preoperative variables associated with T2DM resolution. The following model-building strategy was used. Univariate analysis using logistic regression was applied to identify significant associations with the dependent variable (T2DM resolution). Transformed and untransformed data were used in the analysis. All independent variables with associations of P values of .05 or less then underwent multivariate analysis by simply entering them together using the backward stepwise method. The "best" model for each case definition was based on the strength (Hosmer and Lemeshow goodness-of-fit test), clinical utility, and biologic plausibility of the model. Model parameters were estimated by the maximum-likelihood method. From these estimates, odds ratios with 95% confidence intervals were computed.

The SPSS statistical software program (version 11.0, SPSS Inc., Chicago, IL) was used for all analyses. Statistical significance was set at P less than .05.

RESULTS

The study enrolled 117 consecutive patients over a 30-month period. Ninety-seven patients (83%) completed the 1-year follow-up clinic visit. The mean age was 44.6 $\pm$ 8.3 years, with 79 females and 18 males. Mean preoperative BMI was 49.3 $\pm$ 7.4 (range: 38–78). At 1-year follow-up, the mean EWL was 69.6% $\pm$ 16.3%.

As shown in Table 1, fasting plasma glucose and HbA1C levels significantly decreased after RYGB. However, 6- and 12-month postoperative levels of fasting plasma glucose and HbA1C were similar.

Complete resolution of T2DM was achieved in 72 patients (74%). All of the remaining 25 patients decreased the daily medication requirements (partial resolution). Our cohort of patients was then divided into two groups: (1) complete T2DM resolution (n = 72) and (2) partial T2DM resolution (n = 25). Preoperative demographics, anthropometric

Table 1. Effect of gastric bypass on the glucose metabolism

Variables	Baseline	6 months	12 months	Two-sided *P* value
Fasting plasma glucose mg/dL	164 ± 55*	104 ± 43	101 ± 38	.0001
HbA1C (%)	7.7 ± 1.5	6.1 ± 1.3	6.0 ± 1.1	.0001

HbA1C = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus.
*Preoperative period off T2DM medications.

measures, diabetes-related data, and weight-loss data for the two groups are listed in Table 2. Preoperative waist circumference was a significant predictor for resolution of T2DM. The complete response group had a significantly smaller waist circumference than the partial response group (47.5 ± 3.8 vs. 53.2 ± 3.0; $P = .0001$). Type of medical treatment was also a significant predictor of successful outcome, with patients treated only with oral hypoglycemic medications achieving a higher percentage of complete response than patients treated with insulin. Complete resolution of T2DM was also associated with lower preoperative levels of HbA1C. BMI had a noticeable but not statistically significant effect; patients with a lower BMI achieved a higher percentage of complete response. EWL at 1-year follow-up was similar ($P = .4$) in the two groups (complete resolution: 70.3 ± 17.1; partial resolution: 67.3 ± 19.4).

According to the group's outcome distribution and assumptions of the logistic regression, we entered the two most significant variables into the logistic regression model. We tested the model for goodness of fit using the Hosmer and Lemeshow ($P = .21$) test and concluded that the model fit well. Waist circumference and preoperative treatment without insulin remained significant predictors of T2DM resolution after gastric bypass surgery in the multivariate logistic regression model after adjusting for covariates (BMI, gender, and preoperative HbA1C). As shown in Table 3, for 1-inch change in waist circumference, the associated odds ratio was 2.4. The absence of preoperative insulin treatment increased the chance to have T2DM resolution after RYGB by 42 times. In Figure 1, the calculated probability of T2DM resolution by logistic regression equation is plotted as a continuous dependent variable against the independent variables: waist circumference and preoperative use of insulin.

Table 2. Preoperative demographic, clinical, and laboratory findings

	Complete DM resolution (n = 72)	Partial DM resolution (n = 25)	Two-sided *P* value
Age	44.0 ± 8.9	46.4 ± 6.1	.22
Gender (M/F)	12/60	19/6	.41
No preoperative use of insulin (%)	62/72 (86.1)	8/25 (32)	.0001
BMI (kg/m2)	48.5 ± 7.5	51.7 ± 6.9	.06
Waist circumference (inches)	47.5 ± 3.8	53.2 ± 3.0	.0001
HbA1C (%)	7.5 ± 1.3	8.6 ± 1.7	.001
Duration of T2DM (y)	3.5 ± 2.8	4.3 ± 3.9	.27

DM = diabetes mellitus; BMI = body mass index; HbA1C = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus.

DISCUSSION

The results from our study definitively demonstrate that RYGB achieves better biochemical glycemic control than the most effective medical treatment reported. RYGB induced a significantly greater weight loss, decrement in HbA1C, and decreased requirement for diabetes medications than a low-calorie diet combined with sibutramine treatment.[7] Twelve months after surgery, patients who underwent RYGB experienced a mean HbA1C decrease of 1.7%, and 74% of subjects were not taking any antidiabetic medication. Patients treated with a low-calorie diet and sibutramine experienced a mean HbA1C decrease of 0.6%, and only 26% of subjects were taking reduced doses of diabetes medications; none of the patients were able to discontinue antidiabetic medication.

The relationship between weight loss and improvement in glycemia in subjects with T2DM has not been clearly defined. Caloric restriction and weight loss produce rapid improvements in glycemia, which are mitigated with the passage of time, even when weight loss is maintained.[6,7] Possible explanations for this include acute effects of caloric restriction on glycemia, which lessen as caloric

Table 3. Result of binary logistic regression analysis

Variable	Odds ratio (95% CI)	Coefficient (SE)	Two-sided *P* value
Waist circumference	2.4 (1.4–4.1)	0.9 (0.3)	.001
No preoperative use of insulin	42.2 (4.3–417.3)	3.74 (1.17)	.001

CI = confidence interval; SE = standard error.

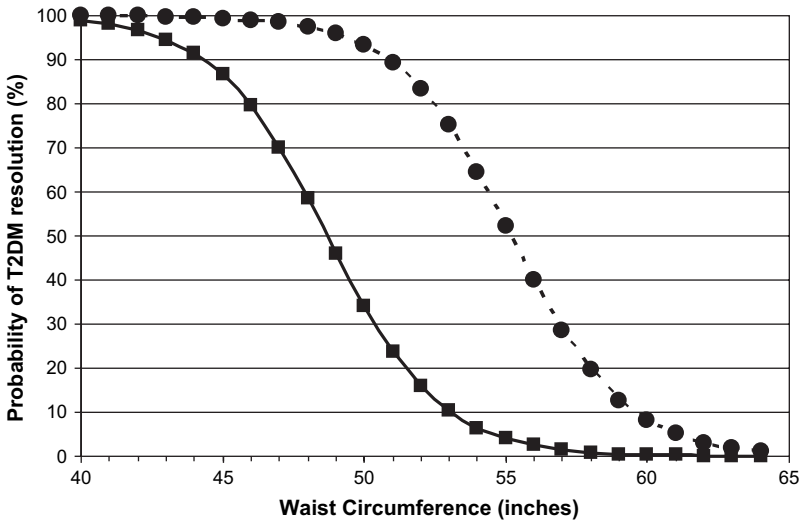

Fig. 1. Prediction of type 2 diabetes mellitus (T2DM) resolution by the logistic regression model. Smooth curves are plots of the probability of T2DM resolution 12 months after Roux-en-Y gastric bypass (RYGB) for patients with (*solid line*) and without (*dotted line*) preoperative insulin use in relation to waist circumference (in inches).

intake returns toward baseline. Currently, bariatric surgery seems to be the only modality that results in sustained weight loss, resolution of diabetes, improvements in cholesterol biosynthesis, lipoprotein metabolism, and decreased cardiovascular risk factors in morbidly obese patients. Long-term follow-up studies by Pories et al[13] showed that patients undergoing RYGB lost 75% of the excess body weight within 24 months, with approximately only a 10% regain after 14 years. The weight loss achieved with RYGB exceeds that with any medical approach, accounting for its higher use in the treatment of morbid obesity. Our results are consistent with recent studies demonstrating significant and sustained improvement in T2DM (up to 10–20 years) after RYGB.[10,11,13] However, direct comparison of these studies can lead to analytic bias because they are different in terms of the study design (retrospective vs. prospective) and methodology of evaluating metabolic outcome by biochemical or clinical assessment. The higher rate of diabetes resolution achieved by Schauer et al.[10] (80%) versus our data (74%) is most readily explained by the exclusion in our series of individual with impaired glucose tolerance (7% in Schauer et al.'s series). In our experience, individuals with impaired glucose tolerance experience early normalization of fasting plasma glucose and HbA1C after RYGB. In our study, the percentage of EWL was similar in patients with resolved and unresolved diabetes. In the Schauer et al.[10] and Sugerman et al.[11] series, the magnitude of EWL positively correlated with T2DM resolution. A plausible explanation of this difference may be that net weight loss may not necessarily be the dominant mechanism driving T2DM resolution because many patients after RYGBP are rendered euglycemic before significant weight loss occurs.

Our study, like others, highlights the pivotal role played by central obesity in the pathogenesis of T2DM. However, we are the first to show that central obesity negatively influences the likelihood of T2DM resolution after RYGB. Not all types of obesity are associated with increased risk of metabolic and cardiovascular complications. Individuals with peripheral fat distribution in the gluteofemoral regions are less prone to develop T2DM and cardiovascular disease than individuals with abdominal fat distribution.[14]

Furthermore, the amount of visceral fat strongly correlates with insulin resistance and can account for most of the variability in insulin sensitivity in the obese population.[15] A major reason behind this correlation is that visceral fat compared with subcutaneous fat is a more important producer of cytokines that are involved in the pathogenesis of insulin resistance.[16,17] In addition, the omentum is the major downloader of free fatty acid into the portal circulation leading to inappropriately elevated hepatic glucose production and hyperinsulinemia.[18] Stolic and coworkers[19] investigated basal and insulin-stimulated deoxyglucose uptake in omental and subcutaneous adipose tissue explants from obese patients. They found that insulin-responsive deoxyglucose transport was significantly lower in the omental adipose tissue of subjects with central obesity, compared with that of subjects with peripheral obesity.

Thorne and coworkers[20] randomized 50 nondiabetic subjects with morbid obesity to either adjustable gastric banding alone or adjustable gastric banding plus removal of the greater omentum (omentectomy). The improvements in oral glucose tolerance, insulin sensitivity, and fasting plasma glucose and insulin were 2 to 3 times greater in omentectomized subjects compared with control subjects. The striking effect of omentectomy on insulin sensitivity raises the argument for removing the omentum during an RYGB in morbidly obese patients with T2DM. We recently started a National Institutes of Health-funded randomized trial aimed to explore the effect of omentectomy combined with RYGB on glucose metabolism. We hypothesize that the combined procedure will be more effective in reversing insulin resistance in obese patients with T2DM than TYGB alone.

CONCLUSIONS

The goal of our study was to determine whether RYGB would result in improved glycemic control in a prospective cohort of morbidly obese subjects with T2DM. The study clearly demonstrated that laparoscopic RYGB is highly effective in achieving excellent glycemic control in patients with T2DM. Six months after surgery, most patients are able to withdraw from all antidiabetic medications including insulin. Improvement in glucose metabolism occurs early after LRYGB and therefore is not entirely related to weight loss. Our study is the first to show that central obesity negatively influences the likelihood of T2DM resolution after RYGB. Last, the comparison of our data with the best results obtained by medical treatment[7] suggests that RYGB should be considered standard treatment of T2DM in morbidly obese patients who are appropriate surgical candidates.

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Discussion

Dr. Jon Gould (Madison, WI): I congratulate Dr. Torquati and his colleagues at Vanderbilt University for conducting this very interesting study. Thank you for getting me the article ahead of time.

As you pointed out, we are currently in the midst of two very closely linked epidemics here in the United States, type 2 diabetes and obesity. These two epidemics are so closely linked, in fact, that the term "diabesity" has been coined. You have demonstrated an impressive 100% response rate of type 2 diabetes to Roux-en-Y gastric bypass in a large prospectively identified cohort. No known medical treatment of type 2 diabetes has demonstrated the kind of consistent results attained in studies such as yours that examine the impact of surgically induced weight loss on this debilitating and progressive disease.

My first question for you is, considering the fact that patient morbidity is significantly decreased with current minimally invasive techniques, why do you think that bariatric technique isn't yet a universally accepted first-line treatment for type 2 diabetes in obese patients in the early stages of this disease?

I have a couple of additional questions. I wonder if you could hypothesize for me an explanation as to why patients with increased waist circumference tend to respond less uniformly to surgically induced weight loss than other patients do.

And finally, I am curious as to the rest of your surgical population, whether your diabetic patients differed from your nondiabetic patients in terms of waist circumference, BMI, age, things like that?

Dr. Torquati: Thank you for your questions. Definitely bariatric surgery is gaining popularity among internal medicine practitioners and the family practitioner, but still there are concerns in terms of morbidity and mortality. Articles like the one recently published by Flum and colleagues, in the *Journal of American College of Surgeons*, report a mortality of 1.75% after bariatric surgery in Washington State. These data support the common opinion of your internal medicine colleagues who consider bariatric surgery still a very risky treatment for this type of patient. Also we don't have level 1 or 2 data regarding the long-term follow-up of these patients in terms of potential weight regain and evolution of comorbidities. I think it is very important for us to continue to follow up patients with type 2 diabetes for 10 and more years after gastric bypass surgery.

For the second question, usually waist circumference is an index of central obesity, and we found that omentum is a very important endocrine organ. Omentum produces a lot of cytokines called adipokines, and we know these are very important in terms of creating the milieu for insulin resistance. Also we know that omentum is a major downloader of free fatty acid to the liver and that high levels of free fatty acid in the portal circulation are associated with insulin resistance.

Regarding the last question, we didn't analyze the data in terms of comparing waist circumference in patients with or without diabetes because our enrolled patients were all diabetic. However, this represents a great idea for a future study.

Dr. Michael Zenilman (Brooklyn, NY): I think this is great that we can now focus on basic physiology rather than the technical issues of bariatric surgery; it has been a long time coming in surgery and medicine. Having Frank Moody and others comment on articles like this is really great.

My question is in terms of the pathophysiology of your observations. Why do you think that actual obesity is the issue? My understanding is that insulin sensitivity and glucose tolerance improve almost immediately after Roux-en-Y bypass surgery; patients can be discharged on less insulin than on admission. Some investigators postulate that incretins secreted from the upper GI tract are involved in this phenomenon. So, why did you study patients at 6 months? You should be looking at this effect a day or two after surgery.

Dr. Torquati: I definitely agree with your statement. We can observe a patient having resolution a few days after gastric bypass surgery. I have a comment that there is an article from Rubino and collaborators, published recently in *Annals of Surgery*, using an animal model showing that you can achieve a very good resolution of diabetes by just bypassing the duodenum and the first portion of the jejunum. I agree with your statement that there is something else that can justify why these patients have resolution of diabetes. It is not only the calorie restriction or the weight loss but some unknown factors that we are looking forward to studying.

Dr. J. Christopher Eagon (St. Louis, MO): Others have shown a relationship between the duration of diabetes preoperatively and its resolution. Did you not see the effect at all or was it not statistically significant in your data?

Did you do any sort of measurements of insulin sensitivity among your patient population, or at least

in subgroups of it? Might insulin sensitivity be a more precise measure than waist circumference?

Dr. Torquati: In previous articles from Schauer and Sugerman, both published in *Annals of Surgery*, short duration of the diabetes was correlated with a good metabolic response to gastric bypass. In our article, we found only a trend, maybe because we had 100 patients compared with the 400 and 500 patients who were included in the Dr. Sugerman and Dr. Schauer article.

It is very important to measure insulin sensitivity in these patients. The best method to assess insulin sensitivity is the minimal model or the insulin clamp study. As you know, they are very invasive studies to perform. Right now in our randomized clinical trial we are assessing insulin sensitivity by insulin clamp studies before surgery and 4 weeks, 3 months, 6 months, and 12 months after surgery. Definitely in the future we are going to have some good data about how insulin sensitivity changes over time.

Dr. Michel Murr (Tampa, FL): I want to echo the previous discussants. I think I would be a little bit more careful about extrapolating resolution of diabetes based on the fasting plasma glucose rather than an invasive test like the intravenous glucose tolerance test. I would look into the just to solidify your argument.

You have shown us that there is a decrease in the plasma glucose and better control of diabetes, and you linked it to central adiposity, but you didn't show us data that the central adiposity has resolved. You only looked at waist circumference. Is there a better way to quantify that?

Dr. Torquati: Regarding the first question, we used the glycosylated hemoglobin as the primary endpoint of your study, not fasting plasma glucose. In fact, low levels of glycosylated hemoglobin have been validated in several studies as an excellent marker of good long-term diabetes control. Regarding the second question, waist circumference has been extensively validated as a great surrogate measurement for central adiposity. However, there is a potential better method: the computed tomography scan of the abdomen with a slice level at the umbilicus. This study allows the measurement of fat distribution between the subcutaneous and intra-abdominal compartment. But this test takes more time and money to do, and at the end, several studies did not provide a better indication of central obesity than waist circumference.

Changes in C-Reactive Protein Predict Insulin Sensitivity in Severely Obese Individuals After Weight Loss Surgery

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The production of inflammatory mediators by abdominal adipose tissue may link obesity and insulin resistance. We determined the influence of systemic levels of interleukin-6 and C-reactive protein on insulin sensitivity after weight loss via Roux-en-Y gastric bypass surgery. Severely obese individuals (n = 15) were evaluated at baseline and at 6 months after surgery. Insulin sensitivity was determined by frequently sampled intravenous glucose tolerance testing at the same time points. Visceral and subcutaneous adipose tissue volumes were quantified by computed tomography. Interleukin-6 and C-reactive protein were measured by enzyme-linked immunoassay in plasma and in adipose tissue biopsies. Correlation analysis was used to determine associations between insulin sensitivity and other outcome variables. Significance was set at $P < 0.05$. Plasma interleukin-6 concentrations were significantly correlated to the IL-6 content of subcutaneous adipose tissue ($r = 0.71$). At 6 months postsurgery, subcutaneous and visceral adipose tissue volumes were significantly reduced (34.7% and 44.1%, respectively) and insulin sensitivity had improved by 160.9%. Significant longitudinal correlations were found between insulin sensitivity and plasma C-reactive protein ($r = -0.61$), but not plasma interleukin-6 at 6 months. These findings offer insights that link obesity and insulin resistance via the activity of inflammatory mediators. (J GASTROINTEST SURG 2005;9:1119–1128) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Insulin resistance, inflammatory mediators, interleukin-6

Insulin resistance, the foundation of metabolic syndrome diseases, is often found in obesity but the links between obesity and insulin resistance are not well defined. Emerging theories suggest that adipose-derived factors, produced in excess by adipose tissue, play a role in the development of obesity-related insulin resistance.[1] These "adipocytokines," including interleukin-6, tumor necrosis factor-alpha, and interleukin-18, are better known for their inflammatory properties as part of the immune system.[2] Of the adipocytokines studied to date, interleukin-6 (IL-6) has the most evidence implicating a role in the development of insulin resistance. Interleukin-6 has been shown to impair glucose uptake in cultured adipocytes in vitro.[3] Also, several cross-sectional studies have demonstrated a relationship between systemic IL-6 concentrations and in vivo measures of insulin sensitivity in humans.[4–7] Furthermore, decreases in plasma IL-6 concentrations were correlated with an improvement in insulin sensitivity during weight loss in three studies.[8–10] In each of these studies, insulin sensitivity was measured using the homeostasis model assessment (HOMA), which is determined from serum concentrations of glucose and insulin in fasting condition. However, HOMA assesses hepatic rather than

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peripheral insulin resistance, which is inadequate because insulin action primarily involves postprandial glucose clearance into muscle and fat. Thus, there is a need for more informative measures regarding the effects of IL-6 on insulin action in vivo with respect to glucose clearance.

Adipose tissue has been shown to be a significant contributor to systemic IL-6 concentrations.[5,11–15] Thus, plasma IL-6 concentrations increase with obesity and decrease with weight loss.[4,7,14,16] We hypothesized that systemic IL-6 concentrations would decrease after weight loss due to decreases in body fat composition. Decreases in IL-6 and other inflammatory mediators may be associated with improvements in insulin sensitivity. We therefore undertook this study to determine the effects of Roux-en-Y gastric bypass surgery-induced weight loss on systemic IL-6 concentrations and adipose tissue production. We also wanted to investigate whether changes in whole body insulin sensitivity are predicted by changes in systemic IL-6 concentrations and C-reactive protein, another marker of inflammation, in severely obese women undergoing weight loss. Weight loss-induced changes in body composition and regional adiposity were determined to assess relationships between inflammatory mediators and insulin sensitivity.

MATERIALS AND METHODS

Patients

Subjects in the study were 15 severely obese female patients undergoing laparoscopic Roux-en-Y gastric bypass surgery (RYGBP) performed as described[17] by surgeons at Emory Endosurgery. The study had a longitudinal design where each patient served as his own control. Subjects were eligible for surgery after preoperative evaluation (clinical, psychological, and nutritional training and assessment) when they were recruited. Exclusion criteria were male gender, age less than 18 years or greater than 65, body mass index less than 35 kg/m^2, smoking, and ineligibility for surgery due to medical reasons. All medication used to treat metabolic syndrome was monitored throughout the study. Records of recent diet history and physical activity were collected at each study visit. The Emory University Institutional Review Board approved the study, and all patients gave informed consent before they were enrolled.

Measurement of glucose tolerance, anthropometry, adipose tissue distribution, and plasma inflammatory biomarkers were obtained at baseline (before surgery), and at 1 month and 6 months postsurgery. The week before baseline and 6 months postsurgery measures were obtained, patients were weight stable, ($\pm$1 kg),[18] and placed on a diet containing sufficient carbohydrates ($\geqslant$150 g) to allow for optimal glucose tolerance testing. These conditions were feasible before surgery and at 6 months postsurgery, but not at 1 month postsurgery when patients were undergoing approximately 3 kg/week weight loss. Records of recent diet history and physical activity were collected at each study visit.

Adipose Tissue Collection

Patients were placed under general anesthesia, and small pieces (1–2 cm^3) of abdominal subcutaneous adipose tissue (SAT) from the region just below the umbilicus, and visceral adipose tissue (VAT) from the omentum, were obtained. Tissues were obtained as the first step of the surgical procedure, once the surgeons had gained access to the respective sites. Adipose tissue was rinsed in phosphate buffered saline (pH 7.4), then rapidly frozen in liquid nitrogen and stored at $-80\,^{\circ}$C.

IL-6 Measurement in Plasma and Adipose Tissue Biopsies

Tissue was homogenized as described[19] in buffer containing 10 mM Tris-HCl, pH 7.4, 250 mM sucrose, and a mixture of protease inhibitors (Complete Midi, Roche Applied Science, Indianapolis, IN). The mixture was centrifuged at 6000 $\times$ g at 22° C for 2 minutes to semipurify adipocytes from macrophages. Upper fat layers were transferred to a new centrifuge tube and the centrifugation step was repeated. Samples of AT homogenate (100 µl) were used to determine IL-6 content using enzyme-linked immunoassay (ELISA, Quantikine High Sensitivity IL-6; R&D Systems, Minneapolis, MN). The inter-assay and intra-assay coefficients of variation and the detection limits for IL-6 were, respectively, 7.2%, 7.8%, and 0.156 pg/ml. Protein content in tissue homogenates was determined using Micro BCA (Pierce Biotechnology, Rockford, IL). Interleukin-6 content in fat was expressed per mg of protein of subcutaneous or visceral adipose tissue. With patients under anesthesia, blood samples were collected at the start of surgery (at the same time as adipose tissue biopsy). Interleukin-6 was measured in plasma samples using the described ELISA kits.

Anthropometry, Body Composition, and Fat Distribution

Body fat composition was measured by air plethysmography (BOD-POD, Life Measurement

Instruments, Concord, CA). Abdominal fat distribution was measured by computed tomography, using a GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI) as described.[20] Volumes of visceral and subcutaneous fat were determined from number of scans taken from the L1 to the L5 vertebral region (140 kV, 240–340 mA, 10 mm slice thickness). Adipose tissue within an attenuation range of −190 to −30 Houndsfield units was highlighted and computed using software (GE Medical Systems). Sagittal abdominal diameter was obtained at the L4-L5 intervertebral space using an abdominal caliper.[21] Body height was measured without shoes. Body weight was measured with subjects in light clothing, in fasting state, and immediately after voiding in the morning. Waist circumference was obtained by tape measure at 2.54 cm above the iliac crest, whereas hip circumference is determined as the maximum value over the buttocks. Thigh circumference was determined at the level midway between the midpoint of the inguinal crease and the proximal border of the patella.

Glucose Tolerance Tests

Insulin action was assessed via the frequently sampled intravenous glucose tolerance test (FSIGTT). Patients were admitted into the Emory General Clinical Research Center on the night before FSIGTT testing and fasted overnight (12 hours). An intravenous catheter was inserted into an antecubital vein for blood sampling. Baseline samples were obtained at −15 and −5 minutes. Glucose (0.3g/kg body weight, as dextrose 50 g/dL) was administered within 2 minutes, and subsequent samples were obtained at 2, 4, 6, 8, 10, 14, 19, 22, 24, 27, 30, 40, 50, 70, 90, 120, 150, 180, 210, and 240 minutes, relative to the start of glucose infusion. At each time point, a 5 ml blood sample was collected. To compensate for possible inadequate endogenous insulin response, at 20 minutes, subjects received an intravenous bolus of human insulin (0.03 U/kg body weight). Plasma was separated and immediately used for glucose and insulin determinations. Minimal modeling[22] was used to quantify several important measures of insulin action in vivo; insulin sensitivity (Si), insulin secretion (AIRg), and the constant, disposition index (DI) using MinMod Millennium (MinMod Inc., Los Angeles, CA). Measures of HOMA insulin resistance were calculated using fasting insulin (μiU/ml) × fasting glucose (mM)/22.5.

Metabolic Measures

Blood was obtained before the start of the FSIGTT, and plasma was separated and stored at −80° C until analysis. Insulin and glucose were quantified at the Emory University Core Laboratory using the Beckman Coulter DX1 and Beckman Coulter Alex 20 automated systems, respectively (Beckman Coulter, Brea, CA). The limit of the assay for insulin was 1 μU/ml and that for glucose was 0.17 mM. High-sensitivity C-Reactive protein was measured using the SYNCHRON LX20 high-sensitivity immunoassay (Beckman Coulter). The sensitivity of the assay is 0.07 mg/dL. Free fatty acids were measured by ARUP Laboratories (Salt Lake City, UT). Free cortisol was measured from urine collected over a 24 hour period, which began at 6:30 A.M. Measurement was performed by ARUP Laboratories and the sensitivity of the assay was 2 mg/L.

Statistical Analysis

The statistical software STATISTICA (StatSoft Inc., Tulsa, OK) was used for analysis. The differences between baseline, 1 month, and 6 months post-surgery measures were analyzed using *t*-tests. The relationship between changes in Si, AIRg, DI, and changes in various metabolic and anthropometrical parameters was determined using linear correlations. In most cases, the data did not follow a normal distribution and nonparametric analysis was used. For comparisons of IL-6 concentrations in plasma and in adipose tissue, data were analyzed using the Mann-Whitney U test for between-group comparisons, and Wilcoxon Matched Pairs test for the within-group comparisons. Correlations between vari ables were calculated by the Spearman Rank Order Test. The significance level was set at $P < 0.05$. Results are expressed as mean ± SEM.

RESULTS

Visceral and Subcutaneous Adipose Tissue IL-6 Content

Adipose tissue biopsies were obtained from abdominal visceral and subcutaneous sites at the start of surgery. Subcutaneous and visceral adipose tissue contained comparable amounts of IL-6 (15.10 ± 4.79 and 12.49 ± 3.50 pg/mg, respectively, $P > 0.05$; data not shown).

Correlation Between Adipose Tissue IL-6 Content and Circulating IL-6

There was a strong positive correlation between the abdominal subcutaneous fat IL-6 content of individual and systemic concentrations of IL-6 in the same subject ($r = 0.71$, $P < 0.005$; Fig.1). Visceral

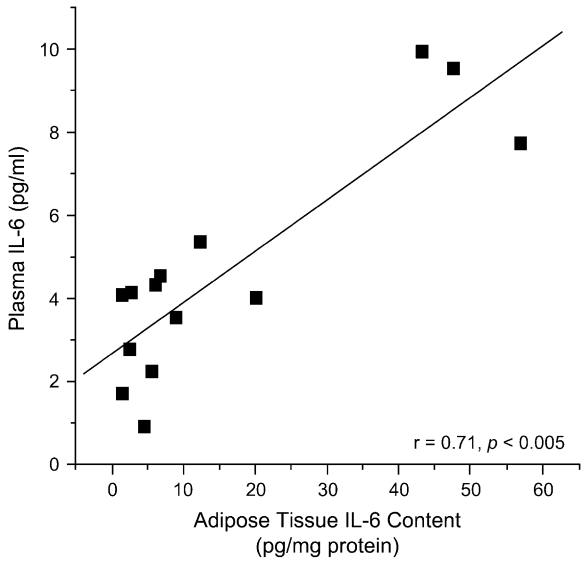

Fig. 1. Positive correlation between abdominal subcutaneous adipose tissue IL-6 content and plasma IL-6 concentrations in individual patients. Blood samples and visceral and subcutaneous adipose tissue biopsies were obtained from severely obese patients (n = 14) at the start of elective surgery procedures. There were significant ($P < 0.05$) positive correlations between plasma IL-6 concentrations and subcutaneous ($r = 0.71$), but not visceral ($r = 0.25$), adipose tissue IL-6 content. IL-6 = interleukin-6.

adipose tissue IL-6 content was not significantly correlated to plasma concentrations of IL-6 ($r = 0.26$, $P > 0.1$).

Baseline and Post Weight Loss Characteristics

Fifteen severely obese women completed analysis from baseline to 6 months after Roux-en-Y gastric bypass. The average age was 35.1 ± 2.1 years. Subjects had two aspects of metabolic syndrome (i.e., dyslipidemia, abdominal obesity, hypertension, hyperglycemia) on average upon entering the study. Two patients had diabetes and were taking insulin sensitizers when their baseline and 1 month postsurgery measures were obtained, but had discontinued their medication by their 6-month postsurgery assessment. Three women in the study were postmenopausal and testing was not done while patients were menstruating.

Baseline anthropometry and changes from baseline after RYGBP are presented in Table 1. Subjects experienced significant decreases from baseline in body mass index (−9.2%), body weight (−9.3%), fat mass (−12.0%), subcutaneous adipose tissue volume (−6.0%), visceral adipose tissue volume (−12.4%), waist circumference (2.5%), and sagittal abdominal diameter (6.4%) at 1 month after weight loss surgery. At 6 months after surgery, subjects experienced significant changes from baseline in body mass index (−25.3%), body weight (−25.6%), fat mass (−39.8%), subcutaneous adipose tissue volume (−34.7%), visceral adipose tissue volume (−44.1%), waist circumference (−13.6%), and sagittal abdominal diameter (20.9%).

Anthropometric changes after surgery were accompanied by metabolic changes including those indicative of metabolic syndrome (Table 2). At one month after RYGBP, subjects experienced significant decreases from baseline values in fasting glucose (−20.1%), fasting insulin (−61.6%), and the HOMA index measure of insulin resistance (−56.9%). Patients also experienced significant improvements in triglycerides (−13.5%) and low-density lipoproteins (LDL, −20.2%), but a worsening of high-density lipoprotein (HDL, −19.3%) and free fatty acids (+44.9%). At 6 months after surgery, subjects showed a significant decrease in systolic blood pressure (−6.8%), and maintained or further decreased from baseline the values in fasting glucose (−18.8%), fasting insulin (−61.6%), and the HOMA index (−68.4%) observed after the first month after surgery. Likewise, the decreases from baseline in triglycerides and LDL observed at 1 month were maintained at 6 months postsurgery. HDL and free fatty acid concentrations, which had worsened at 1 month postsurgery, were restored to baseline levels at 6 months after surgery. There were no significant changes observed in diastolic blood pressure at 1 month or 6-month post-RYGBP.

Correlations Between Adipose Tissue Volumes and Inflammatory Mediators

We determined relationships between visceral and subcutaneous adipose tissue volumes and inflammatory mediators IL-6 and C-reactive protein at baseline and after 6-month weight loss using linear correlations. There were strong correlations between visceral adipose tissue volumes and plasma IL-6 concentrations ($r = 0.52$, $P = 0.037$), as well as between subcutaneous adipose tissue volumes and IL-6 concentrations ($r = 0.48$, $P = 0.056$) at 6 months after weight loss surgery; however, these relationships were not observed at baseline (data not shown). There were no significant correlations observed between abdominal adipose tissue volumes and C-reactive protein (data not shown).

Correlations Between Insulin Sensitivity and Inflammatory Mediators

Linear correlations between changes in insulin sensitivity and corresponding changes in anthropometry

Table 1. Anthropometric changes in severely obese women following Roux-en-Y gastric bypass surgery

	Before surgery	1 mo postsurgery	6 mo postsurgery
BMI (kg/m^2)	48.5 ± 0.9	44.0 ± 0.9‡ (−9.2%)	36.3 ± 0.9‡ −25.3%
Weight (kg)	127.3 ± 2.3	115.2 ± 2.3‡ (−9.3%)	94.5 ± 2.5‡ −25.6%
Fat mass (kg)	72.0 ± 2.1	63.5 ± 1.9‡ (−12.0%)	43.5 ± 1.9‡ −39.8%
SAT (cm^3)	$1.34 \times 10^4 \pm 0.045 \times 10^4$	$1.25 \times 10^4 \pm 0.03 \times 10^4$* (−6.0%)	$0.890 \times 10^4 \pm 0.060 \times 10^4$‡ −34.7%
VAT (cm^3)	$3.88 \times 10^3 \pm 0.46 \times 10^3$	$3.53 \times 10^3 \pm 0.45 \times 10^3$† −12.4%	$2.07 \times 10^3 \pm 0.27 \times 10^3$‡ −44.1%
Waist (cm)	137.2 ± 3.1	132.8 ± 3.1* −2.5%	118.2 ± 3.2* −13.6%
SAD (cm)	30.7 ± 0.6	28.6 ± 0.7† −6.4%	24.1 ± 0.7‡ −20.9%

Values are ± SEM, percent changes are from baseline.
*$P < 0.05$.
†$P < 0.005$.
‡$P < 0.0005$.
BMI = body mass index; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; SAD = sagittal abdominal diameter.

Table 2. Metabolic changes in severely obese women following Roux-en-Y gastric bypass surgery

	Before surgery	1 mo postsurgery	6 mo postsurgery
SBP (mmHg)	136 ± 5.8	125.9 ± 4.8 −5.3%	122.3 ± 4.6* −9.1%
DBP (mmHg)	79.3 ± 2.7	77.1 ± 3.8 −0.7%	73.4 ± 2.9 −6.3%
Glucose (mM)	5.41 ± 0.38	4.17 ± 0.14† −20.11%	4.21 ± 0.09† −18.8%
Insulin (μU/ml)	13.88 ± 1.84	7.44 ± 1.11‡ −44.6%	4.67 ± 0.77‡ −61.6%
HOMA ($mM \cdot \mu U \cdot ml^{-1}$)	3.56 ± 0.51	1.46 ± 0.24‡ −56.87%	0.89 ± 0.16‡ −68.4%
LDL (mg/dl)	97.6 ± 8.0	76.0 ± 6.5† −20.2%	75.0 ± 5.3† −21.8%
HDL (mg/dl)	44.0 ± 2.5	34.7 ± 2.3† −19.3%	40.9 ± 1.9 −5.6%
Triglycerides (mg/dl)	115.6 ± 17.8	91.3 ± 9.4* −10.9%	92.0 ± 15.1* −20.2%
Free fatty acids (mM)	0.72 ± 0.05	1.01 ± 0.06† 44.9%	0.78 ± 0.05 15.9%
Si (Si units)	1.77 ± 0.23	2.17 ± 0.39 31.8%	2.65 ± 0.25* 160.9%
CRP (mg/dl)	1.36 ± 0.31	1.07 ± 0.22 −0.01%	0.65 ± 0.19* −46.0%
IL-6 (pg/ml)	4.92 ± 0.67	5.51 ± 1.02 −2.9%	3.47 ± 0.37† −13.8%

Values are ± SEM, percent changes are from baseline.
*$P < 0.05$.
†$P < 0.005$.
‡$P < 0.0005$.
SBP = systolic blood pressure; DBP = diastolic blood pressure; HOMA = homeostasis model assessment; LDL = low-density lipoproteins; HDL = high-density lipoproteins; CRP = C-reactive protein; IL-6 = interleukin-6.

and metabolic variables during weight loss were determined (Table 3). There were weak, nonsignificant, negative correlations between changes in Si and changes in body fat, visceral fat volume, subcutaneous fat volume, and sagittal abdominal diameter. There was also a nonsignificant negative correlation between changes in Si and changes in IL-6, although there was a strong correlation ($r = -46$) between plasma IL-6 concentrations and Si at 6 months postsurgery, which tended toward significance ($P = 0.081$). However, during the 6-month weight loss period, we observed a significant negative correlation between changes in insulin sensitivity and changes in the inflammatory mediator C-reactive protein ($r = -0.71$, $P < 0.005$; Fig. 2).

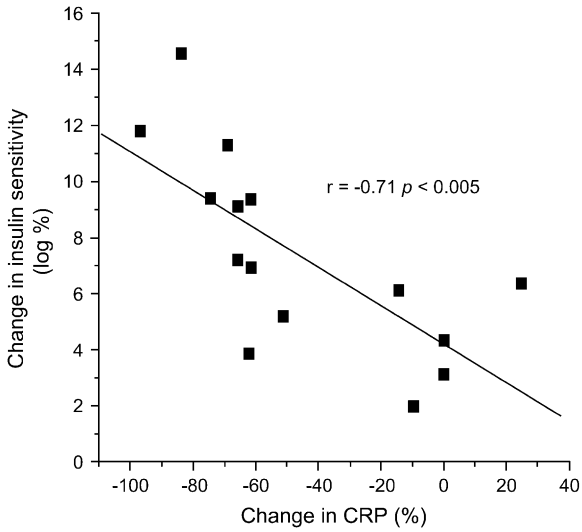

Fig. 2. Negative correlation between changes in C-reactive protein (CRP) and changes in insulin sensitivity from baseline to six months post surgery. Insulin sensitivity was measured in severely obese women via frequently sampled intravenous glucose tolerance test before and at 6 months following Roux-en-Y gastric bypass surgery. Corresponding plasma measures of CRP were determined by high-sensitivity ELISA assay. Percent changes from baseline in CRP were negatively correlated to percent changes in insulin sensitivity over the same time period ($r = -0.71$, $P < 0.005$). CRP = C-reactive protein.

DISCUSSION

This is the first longitudinal study to investigate whether measures of abdominal obesity are related to circulating concentrations of IL-6 and C-reactive protein, as well as to whole body insulin sensitivity. The main finding was that changes in inflammatory mediators are negatively correlated to changes in insulin sensitivity in severely obese women undergoing weight loss after Roux-en-Y gastric bypass surgery. We also show that production of IL-6 in abdominal subcutaneous adipose tissue explants is positively correlated with—and therefore contributes to—circulating concentrations of IL-6.

Plasma IL-6 concentrations have been shown to be correlated positively with body mass index in several studies,[4,5,16] and it has been recently shown that IL-6 is produced in adipose tissue by adipocytes, stromal cells, and macrophages.[13,23] The correlations we observed between adipose tissue production of IL-6 and plasma IL-6 concentrations suggest that abdominal subcutaneous adipose tissue-derived IL-6 accounts for 50% of plasma IL-6 levels. Macrophages, lymphocytes, and tissues such as liver also produce IL-6.[24–26] However, the high correlations between plasma IL-6 concentration and fat IL-6 production, when measured directly in adipose tissue biopsies, strongly suggests that abdominal adipose tissue IL-6 production is a strong determinant of circulating IL-6 concentrations. In this study, we found that systemic IL-6 concentrations decreased with weight loss. Although we did not repeat adipose tissue biopsy after weight loss, in a prospective study, Bastard et al.[19] demonstrated that subcutaneous adipose IL-6 content was decreased after weight loss. Moreover, we did find that systemic IL-6 concentrations were decreased at 6 months after surgery after significant reduction in subcutaneous and visceral adipose tissue as well as total body fat. Taken together, this data supports our conclusion that adipose tissue IL-6 production strongly contributes to circulating IL-6 concentrations.

Studies have examined the secretory functions of abdominal visceral and subcutaneous adipose tissue to determine the roles of these depots with regard to the etiology of metabolic complications related to obesity. At baseline, we did not find differences in

Table 3. Correlations between changes in Si and changes in anthropometry and metabolic variables

	r	*P* value
BMI	0.082	0.77
Fat	−0.021	0.94
VAT	−0.20	0.47
SAT	−0.29	0.28
Weight	0.09	0.74
SAD	−0.02	0.77
WC	0.09	0.69
IL-6	−0.15	0.58
CRP	−0.71	0.003

VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; CRP = C-reactive protein; IL-6 = interleukin-6.

adipose tissue IL-6 production when comparing subcutaneous and visceral biopsies taken from severely obese individuals. Fried et al[12] reported that IL-6 release from visceral adipose tissue biopsies obtained from SO individuals was greater compared to IL-6 release from subcutaneous adipose tissue biopsies obtained from the same patients. A recent study by Fain et al[13] found greater IL-6 release from visceral versus subcutaneous adipose tissue explants obtained from obese humans; however, when comparing adipocytes obtained from visceral and subcutaneous adipose tissue depots, release of IL-6 was similar. In obese rats, higher IL-6 content and mRNA expression was observed in visceral, compared with subcutaneous, adipose tissue.[27] With regards to the obese state at baseline, the discordance between our findings and those from other studies reported above may be due to differences in methodology used to evaluate IL-6 production rates; our study addressed ex vivo IL-6 content within adipose tissue, whereas other studies have determined in vitro IL-6 secretion by adipose tissue in the culture media. Ex vivo IL-6 measurement would reflect the content of IL-6 in adipose tissue at the time of biopsy, rather than the de novo synthesis in vitro. Interleukin-6 production rates in vitro may be influenced by environmental triggers, such as a change in atmospheric O_2,[28] and/or removal of in vivo factors that influence IL-6 release.

Inflammatory mediators have been associated with measures of resistance in cross-sectional studies.[4–7] Often insulin action is estimated using the HOMA index, which is more reflective of insulin resistance in the liver but not insulin sensitivity in peripheral tissues (skeletal muscle and adipose tissue). This study is the first to determine the relationships between IL-6 and whole body insulin sensitivity measured by intravenous glucose tolerance testing. Our findings suggest that although IL-6 was negatively correlated with insulin sensitivity at 6 months after weight loss, it did not appear to be a predictor of changes in insulin sensitivity. Plasma C-reactive protein was the only significant predictor of insulin sensitivity and changed in parallel with insulin sensitivity during weight loss. In support of our finding, others have reported correlations between measures of insulin resistance and C-reactive protein concentrations;[29–31] however, these correlations were not determined longitudinally. In this study, changes in overall adiposity such as body mass index and fat mass, and changes in abdominal obesity, were not significantly associated with changes in insulin sensitivity. This finding suggests that the longitudinal relationship between plasma C-reactive protein and insulin sensitivity is independent of changes in obesity. In support of this finding, in this study we did not find correlations between abdominal adiposity and plasma C-reactive protein. Changes in abdominal adiposity have been associated with changes in insulin sensitivity in several studies. Given that the sample size of this study is small (n = 15), it will be important to determine if the associations between insulin sensitivity and abdominal adiposity as well as C-reactive protein remain the same as the sample size of our study increases. Further studies should assess whether the relationships between changes in adiposity and changes in insulin sensitivity are altered in patients who undergo surgically induced weight loss by including patients who undergo diet-induced weight loss. Finally, we recognize the importance of determining changes in the plasma and adipose tissue profiles of other adipocytokines, including adiponectin, resistin, tumor necrosis factor, and leptin before and during weight loss, because these factors have been shown to play a role in insulin action.[5,32–34]

This study demonstrates production of IL-6 by abdominal adipose tissue contributes, in part, to circulating IL-6 concentrations in severely obese individuals. At 6 months after Roux-en-Y gastric bypass, measures of visceral and subcutaneous adiposity as well as whole body obesity were significantly decreased compared to baseline measures. These changes were accompanied by decreases in IL-6 and C-reactive protein, and improvements in insulin sensitivity. However, the inflammatory mediator C-reactive protein was the strongest predictor of changes in insulin sensitivity— independent of changes in obesity.

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Discussion

Dr. Michael Meguid (Syracuse, NY): Thank you, Dr. Gletsu, for sending me your manuscript. My comments address essentially two points.

First, you showed an improvement in insulin sensitivity using frequent sampling intravenous glucose tolerance tests (FSIVGTT) after RYGB-induced weight loss at 1 and 6 months and that this was accompanied by a more rapid decrease in VAT than SC-AT, which is a recurring observation suggesting that VAT is more labile and quantitatively contributes greater to improvement in glucose intolerance and insulin resistance, both of which are hallmarks of the metabolic syndrome. No doubt you are aware that using FSIVGTT also measures beta cell function, plasma glucose clearance, and hepatic glucose utilization, which improved with your observed weight loss at 6 months. These points should be considered when interpreting your improvement in glucose intolerance and insulin sensitivity. Other contributory causes include the significant increases in muscle insulin receptors, as documented by Pander et al in 2004, one year after Roux-en-Y gastric bypass (RYGB). Lastly, a rise in adiponectin after RYGB also enhances glucose tolerance by improving insulin sensitivity, and although you did not measure adiponectin, based on your data of post-operative fall in HDL at 1 and 6 months, I infer from your paper that adiponectin must have risen in your patients because adiponectin inversely correlates with plasma HDL concentrations. Thus, the rise in adiponectin would be another reason whereby insulin sensitivity improved in your patients.

Second, cytokines play a critical role in the insulin resistance of obesity. Whereas our group showed an increase in tissue VAT IL-6 and corticosterone concentrations, you elegantly showed an increase in circulating plasma IL-6 that correlated directly with VAT IL-6 content in your obese patients preoperatively. Postoperatively, your patients lost VAT. Did you then measure and correlate IL-6 and VAT? You may not have had the opportunity to reoperate on these patients to obtain further VAT or further blood samples so as to measure tissue and circulating IL-6. Even though it is difficult to obtain intra-abdominal fat after RYGB, it should be possible to obtain subcutaneous fat and thereby establish this correlation. Nevertheless, you correctly inferred and linked the connection between IL-6 and VAT after weight loss, because insulin sensitivity and CRP improved in your patients with weight loss. Vasquez et al in 2005 also reported a decrease in CRP after weight loss, but circulating levels of IL-6 and TNFα did not change. Lastly, I wonder if you measured serum or tissue resistin concentration. Resistin is another adipokine secreted by the adipocyte and by migrating monocytes into the fat tissue of obese patients. It is secreted in response to elevated IL-6 and TNFα and increases insulin resistance. Obviously, there is a complex overlap between obesity and the inflammatory system leading to insulin resistance, whose mechanism is important to understand because it affects the health of 50% of our population. Thank you for asking me to comment on your paper and I encourage you to pursue your very interesting research.

Dr. Gletsu: Thank you, Dr. Meguid, for agreeing to be a discussant. We measured urinary cortisol because we were trying to find out the other hormones that might affect insulin function, corticosteroids, and hormones of that nature. So we actually determined that there were no changes in urinary cortisol between the baseline one-month and six-month period, which looked like we weren't having too many effects of counter-regulatory hormones during the time that we were doing the glucose tolerance test, which is interesting. We also measured free fatty acids to see what effects free fatty acids would have on the glucose tolerance test, and we didn't see any changes from baseline at six months. So again, that is why we measured these variables.

We have measured IL-6 and C-reactive protein, but we also plan on measuring other inflammatory and anti-inflammatory hormones such as IL-18, IL-10, and then based on the comments you had at first, we definitely plan on looking at adiponectin, resistin, and leptin, and the power of, I think, this study will be to determine how each of these hormones change with the weight loss to determine the roles and the interplay between these hormones as insulin sensitivity improves.

As far as menstrual status, most of our patients were premenopausal, and in the small number we had not had any patients who had undergone any hysterectomies. This is why we said that the hormonal status was pretty similar in all of our patients.

Dr. Frank Moody (Houston, TX): In Houston, in collaboration with Heinrich Taegtmeyer, a cardiologist who is an expert in cardiac metabolism, we are studying insulin resistance in cardiomyocytes before and after gastric bypass.

Early in this study, what we are finding is that, before and three months after small pouch gastric

bypass, there actually is quite a significant elevation of TNFα even during rapid weight loss. It is going to be very interesting to see what happens as you analyze for other proinflammatory cytokines. If the proinflammatory cytokines are involved in insulin resistance, what is the mechanism?

Dr. Gletsu: The mechanism might be at the glucose transporter level. There have been some studies to show that some of these cytokines may trigger signaling effects on glucose transporters, or something post-receptor level is what I think the mechanisms are that people are trying to explain for inflammatory mediators.

And as far as your first statement about TNFα, we do plan on measuring TNFα also. It is interesting; patients had sometimes either improved insulin resistance at one month or had a worsened insulin resistance at one month. So it will be interesting to see what TNFα did and what some of these other hormones did to explain some of those measures.

Development of a New Access Device for Transgastric Surgery

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Flexible endoscope–based endoluminal and transgastric surgery for cholecystectomy, appendectomy, bariatric, and antireflux procedures show promise as a less invasive form of surgery. Current endoscopes and instruments are inadequate to perform such complex surgeries for a variety of reasons: they are too flexible and are insufficient to provide robust grasping and anatomic retraction. The lack of support for a retroflexed endoscope in the peritoneal cavity makes it hard to reach remote structures and makes vigorous retraction of tissues and organs difficult. There is also a need for multiple channels in scopes to allow use of several instruments and to provide traction/countertraction. Finally, secure means of tissue approximation are critical. The aim was to develop and test a new articulating flexible endoscopic system for endoluminal and transgastric endosurgery. A multidisciplinary group of gastrointestinal physicians and surgeons worked with medical device engineers to develop new devices and instruments. Needs assessments and design parameters were developed by consensus. Prototype devices were tested using inanimate models until usable devices were arrived at. The devices were tested in nonsurvival pigs and dogs. The devices were accessed through an incision in the wall of the stomach and manipulated in the peritoneal cavity to accomplish four different tasks: right upper quadrant wedge liver biopsy, right lower quadrant cecal retraction, left lower quadrant running small bowel, and left lower quadrant exposure of esophageal hiatus. In another three pigs, transgastric cholecystectomy was attempted. The positions of the device, camera, and endosurgical instruments, with and without ShapeLock technology, were recorded using laparoscopy and endoscopy and procedure times and success rates were measured. Instrument design parameters and their engineering solutions are described. Flexible multilumen guides which could be locked in position, including a prototype which allowed triangulation, were constructed. Features of the 18-mm devices include multidirectional mid body and/or tip angulation, two 5.5-mm accessory channels allowing the use of large (5-mm) flexible endosurgical instruments, as well as a 4-mm channel for an ultraslim prototype video endoscope (Pentax 4 mm). Using the resulting devices, the four designated transgastric procedures were performed in anesthetized animals. One hundred percent of the transgastric endosurgical procedures were accomplished with the exception of a 50% success for hiatal exposure, a 90% success rate for wedge liver biopsy, and a 33.3% success rate for cholecystectomy. A new endosurgical multilumen device and advanced instrumentation allowed effective transgastric exploration and procedures in the abdominal cavity including retraction of the liver and stomach to allow exposure of the gallbladder, retraction of the cecum, manipulation of the small bowel, and exposure of the esophageal hiatus. This technology may serve as the needed platform for transgastric cholecystectomy, gastric reduction, fundoplication, hiatus hernia repair, or other advanced endosurgical procedures.
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KEY WORDS: Flexible endoscopy, transgastric surgery, endoluminal, cholecystectomy

In the past 20 years, there has been a steady decrease in the "invasiveness" of surgical interventions. The majority of open surgical procedures have been replicated if not replaced by laparoscopic, interventional radiologic, or flexible endoscopic techniques[1] (Table 1). There is currently interest in further expanding the capabilities of flexible endoscopic surgery (FES) to accomplish procedures that

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Table 1. Some Examples of Open Abdominal Surgeries That Have Been Largely Replaced by Less-Invasive Approaches

Open Procedure	Percutaneous (IR)	Flexible Endoscopy	Laparoscopic
Cholecystectomy			X
Common bile duct stones		X	X
Intra-abdominal abscess	X		
Pancreatic pseudocyst		X	X
GERD treatments		X	X
Appendectomy			X
Bariatric procedures			X
Enteric resection/ anastomosis			X
Hernia repair			X
Palliative bypass of malignant obstructions	X	X	X

GERD = gastroesophageal reflux disease.

currently require laparoscopic access.[2] Procedures that have been theorized as being possible candidates for FES are listed in Table 2. Potential patient advantages to FES include less or no pain, no skin incisions, avoidance of general anesthesia, movement of many procedures to the outpatient arena, and possibly reduced procedure costs. Many technical hurdles need to be overcome before such "incisionless" surgery becomes a reality. We summarize the development of new FES instrumentation and present early laboratory experiences with two new devices based on ShapeLock technology (USGI Medical, San Clemente, CA) that we believe solve several of the technical problems identified by a group of experts and that, therefore, may serve as a "platform" for further progress on complex endoluminal, transgastric, and transcolonic endoscopic procedures.

Table 2. Proposed Advanced Procedures for Flexible Endoscopic Surgery

Route employed	Procedures
Endoluminal	Barrett's ablation
	Antireflux valves
	Mucosectomy
	Full-thickness excisions
	Bariatric procedures
Transgastric/transenteric	Tubal ligation/oopherectomy
	Staging peritoneoscopy
	Cholecystectomy
	Appendectomy
	Hernia repair
	Gastric bypass for obesity
	Enteroenteric anastomoses

METHODS

A physician group teamed with the engineers of a medical device company (USGI Medical) with the goal of designing the appropriate instrumentation and approaches to achieve transluminal FES using the ShapeLock technology (USGI Medical) beginning with the collaborative determination of what would be required to accomplish three signature transgastric procedures: endoscopic staging peritonoscopy, appendectomy, and cholecystectomy. These procedures were chosen to serve as the developmental goals of an instrumentation and approach design protocol. The design team consisted of gastrointestinal surgeons who practiced laparoscopic surgery and flexible endoscopy (L.L.S., S.G., D.B.) and gastroenterologists with a special interest in aggressive endoluminal FES (R.K., P.J.P., P.-O.P., P.S.). The team collaborated to create a list of the design particulars for the conceived instruments as well as a list of the procedure hurdles that needed to be overcome (Table 3). The team met frequently to further test and refine the instrumentation.

Once the prototype instrument set had been developed to the satisfaction of the procedure team, they were taken to the animal lab for testing in inanimate models and, subsequently, in nonsurvival animals. Six 50-kg pigs and four mongrel dogs were used in a series of graduated experiments to examine the capabilities of the instruments. The animal studies were conducted in accordance with U.S.D.A. Animal Welfare Act and approved by the Institutional Animal Care and Use Committee. All animals were anesthetized and positioned supine. In the porcine model, the esophagus was isolated through a longitudinal neck incision and the FES devices inserted directly via an esophagotomy. The devices were inserted per os in the canine model. All animals had a 5-mm laparoscope port inserted into the gastric fundus to record the intragastric movements of the FES scopes and instruments. The animals also had laparoscopic ports placed in the low abdomen to allow the FES devices to be viewed and their movements recorded. The FES devices were advanced into the stomach and were configured into both antegrade and retroflexed positions. The ability of different grasper designs was tested by attempting to grasp and imbricate the stomach wall. A variety of tissue approximation devices were tested by

approximating adjacent folds of gastric fundus and by approximating the lesser and greater gastric curvature at the gastroesophageal junction. Following this, a gastrotomy was created in the anterior gastric wall using standard energy sources, and the FES devices were advanced into the peritoneal cavity once it was insufflated. Peritonoscopy was modeled by positioning the FES devices in each of the four abdominal quadrants. Various manipulations were performed including wedge liver biopsy, bowel manipulation, cecal retraction, and exposure of the esophageal hiatus. In three animals, the gallbladder was exposed and retracted, the cystic artery and duct were dissected and divided, and removal of the gallbladder was attempted in a standard retrograde fashion. Finally, the device was withdrawn into the stomach and the gastrotomy was closed. Data collected were the success of the individual maneuver, the time that the procedure required, and device success or failure.

RESULTS

Technology

The following instrument design needs were identified to attempt to resolve the technical goals as they were initially identified by the team (Table 3).

Size—Problem. The new instrument must be small enough for routine transoral insertion and yet have at least three large (3- to 6-mm) channels.

Solution. The FES guides are 18 mm in maximum diameter. The tip is slightly tapered to allow easy insertion.

Image— Problem. The video-optics must be of sufficient resolution to allow complex repairs and identification, and the light transmission must be sufficient to illuminate the insufflated abdominal cavity.

Solution. Imaging is provided by a prototype 4-mm Pentax flexible scope inserted through a 6-mm access lumen. The scope is a digital, 4-mm "chip-on-a-stick" 160-cm length scope that provides excellent illumination and resolution and has two-way tip deflection.

Table 3. Consensus Determination of the Most Critical Design Requirements for Flexible Endoscopic Transgastric Surgery

Stable platform
Organ retraction
Secure grasping
Energy source
Triangulation
Tissue approximation

Insufflation—Problem. High-flow CO_2 insufflation is required to establish a safe pneumoperitoneum and to maintain intragastric visualization while closure of the gastrotomy is performed.

Solution. CO_2 insufflation from a standard 20-L high-flow laparoscopic insufflator (Stryker, Kalamazoo, MI) is applied via an adaptor on the device which allows insufflation through one of the small lumens in the guide.

Suction/irrigation—Problem. Complex procedures require the ability to readily clear blood and fluid from the field to a greater extent than standard flexible scopes.

Solution. Suction and irrigation is performed through another small lumen in the guide and is controlled by a trumpet valve adapted from laparoscopy.

Incision—Problem. Tissue and suture material needs to be reliably cut, hemostatically when required.

Solution. Standard flexible endoscopic energy sources (needle knife, cautery snare) were used for incisions and excisions.

Contamination—Problem. There is a potential risk of peritoneal infection from oral or gastric contamination during transgastric instrumentation.

Solution. These procedures should be considered contaminated procedures. Gastric preparation to ensure no solid contaminants in the stomach is necessary and delayed gastric emptying may be a contraindication for the approach. Prophylactic antibiotics will be indicated and topical antibiotic lavage may be necessary, although open and laparoscopic transgastric procedures usually do not require such extra precautions.

Maneuverability—Problem. Intra-abdominal surgery will require radical positioning such as 180-degree retroflexion.

Solution. Devices are designed with full flexibility including retroflection in two planes and four-way maneuverability at the tip as well.

Stability—Problem. Current flexible scopes are too soft and flexible to allow aggressive tissue manipulation, particularly for organ retraction and anatomical restructuring.

Solution. The transgastric guides are based on the ShapeLock technology (Fig. 1). This allows the scope to have complete flexibility for insertion and positioning but then establish complete rigidity of the entire shaft by compressing a lever. The maneuverable tip remains capable of independent motion to allow fine positioning.

Multi-instrumentation—Problem. Complex endoscopic surgery will require multiple instrument use on a routine basis.

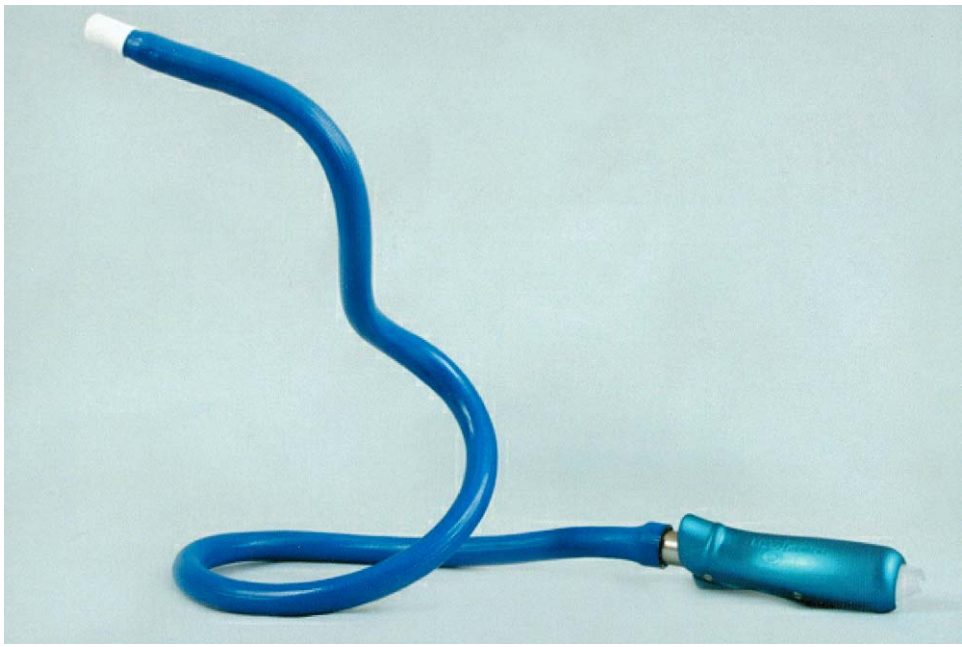

Fig. 1. The basic instrumentation uses the Shapelock technology, which allows an advanced scope to be inserted and positioned while flexible and then locked in place for needed stability.

Solution. Both of the current instruments have multiple channels to permit both an optical device and two instruments up to 5.5 mm. In addition, there are smaller channels that permit insufflation and irrigation.

Triangulation—Problem. Traditional endoscopic surgery relies on the ability to triangulate in order to efficiently visualize and manipulate tissue, particularly for tissue approximation.

Fig. 2. Multiple large lumens, one for a 4-mm flexible optic, are available, and one device has independently moveable arms to allow triangulation and complex actions.

Solution. The steerable ShapeLock-based device has parallel ports like standard flexible scopes, but its larger size (18 mm) separates the working instruments to some extent. To increase the capabilities of the instrument, a second device was designed with three independent arms at the tip that permit optimal positioning of the optics and complex independent maneuvers with the endoscopic instrumentation (Fig. 2).

Retraction—Problem. To perform intra-abdominal surgeries, there is a need to retract organs and/or intestines to provide exposure. This requires strong grasping tools and the ability to hold even a large organ like the liver out of the way.

Solution. The large operating channels of the current devices have allowed the design and use of more substantial and aggressive grasping tools. In addition, the rigid locking shaft of the devices can be used to leverage and hold solid organs anteriorly (Fig. 3).

Hemostasis—Problem. Meticulous hemostasis is critical in any endoscopic procedure as bleeding rapidly obscures visualization and is difficult to control.

Solution. Standard endoscopic methods of hemostasis (cautery and clips) have proved to be sufficient in the laboratory experience to date.

Closure of exit enterotomy—Problem. A critical element of any transluminal FES is the ability to securely close the organ exit site. This could be done with a closure device or by tissue approximation techniques.

Solution. We used several innovative endoscopic suturing devices to approximate tissues and close the exit site following transluminal FES. Only the Bard Endocynch (Conmed Medical) is currently commercially available.

Laboratory Experience

Both FES devices were successfully inserted in all 10 animals without mucosal injury. The scopes were able to be positioned in the stomach, in both an antegrade and a retrograde position, and locked in place. Tissue retraction was best achieved either with the most aggressive 4-mm grasper or with a 2-mm "corkscrew" device. A gastrotomy was created without bleeding in any animal, and the device and scope were successfully advanced into the abdomen. The device was able to be directed to all four quadrants of the abdomen and locked into place using the Shapelock technology. In the right lower quadrant, the cecum was identified, grasped, and raised anteriorly. In the left lower quadrant, the small bowel was grasped and run for several centimeters using two graspers. The right upper quadrant was successfully viewed by retroflexion in all animals. A wedge liver biopsy was attempted and accomplished in nine animals using a grasper and monopolar cautery. In one

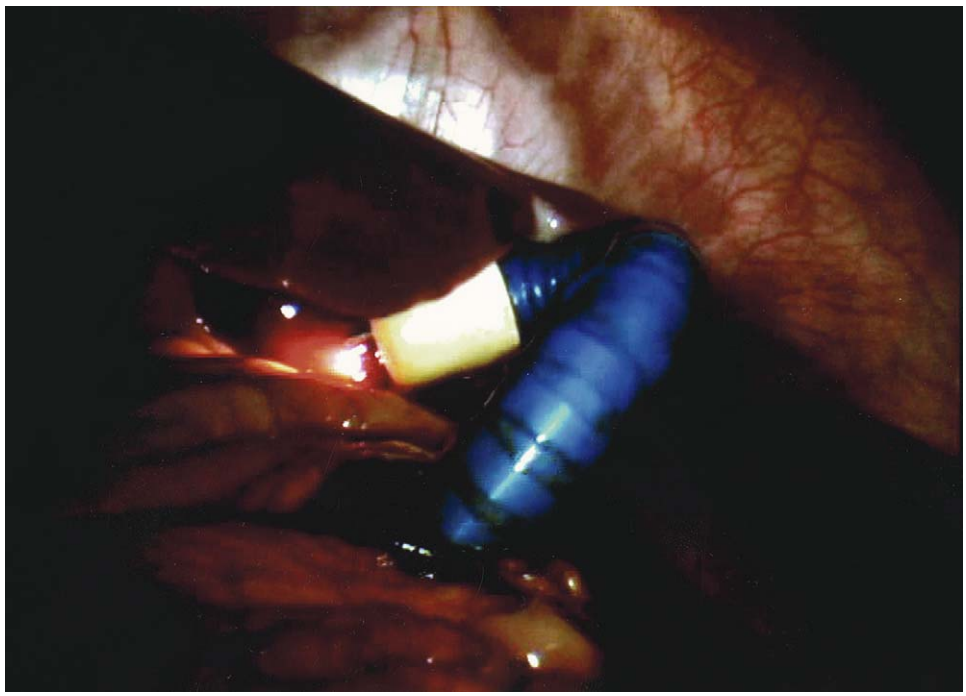

Fig. 3. Upper abdominal exposure is obtained by supporting the liver (or other organs) on the shaft of the stiffened device, while the tip remains able to be freely maneuvered.

animal, significant bleeding was encountered that was not able to be stopped with cautery or endoscopic clips and required a laparoscopic "rescue." In the left upper quadrant, access to the esophageal hiatus was attempted by retroflexing the scope, maneuvering it under the left liver lobe and using reverse Trendelenburg position to "retract" the spleen downward. This allowed successful identification of the gastroesophageal junction in two pigs (33%) and three dogs (75%). Finally, exposure and dissection of the gallbladder were attempted in three pigs. This was done in retroflexion with the locking body of the device used to hold up the liver (Fig. 3). Aggressive graspers were used to retract the infundibulum and a needle-knife cautery (Boston Scientific) was used to dissect the cystic duct and artery as well as mobilize the gallbladder off the liver bed (Fig. 4). Cystic arteries were controlled with endoscopic clips (Boston Scientific). The mobilized gallbladder was then withdrawn back into the stomach as the device was withdrawn. The entire procedure was successfully accomplished in one of the three animals. In one animal, bleeding from the cystic artery was unable to be controlled and visualization was lost. In the second animal, perforation of the gallbladder occurred and made identification of the dissection planes impossible so the attempt was abandoned. In the third animal, the gallbladder was successfully removed, although perforations occurred, and was withdrawn into the stomach. This portion of the procedure, from exposure to placement into the stomach, took 56 minutes.

Gastrotomy closure was attempted in six animals. Two different closure devices were used; a tissue anchoring system in four and a variation of the Bard suturing device in two. Neither of the devices used are commercially available. Closure was completed in five of six attempts but was watertight on explant testing only in one stomach. Results of the animal studies are summarized in Table 4.

DISCUSSION

Advanced flexible endoscopic surgery is becoming a more widely accepted and practiced approach.[3] Endoluminal procedures such as mucosectomy and antireflux procedures are now commonplace.[4–6] More recently, the gastrointestinal barrier has been breeched, with closure of perforations, creation of enteroenteric anastomosis, and other procedures

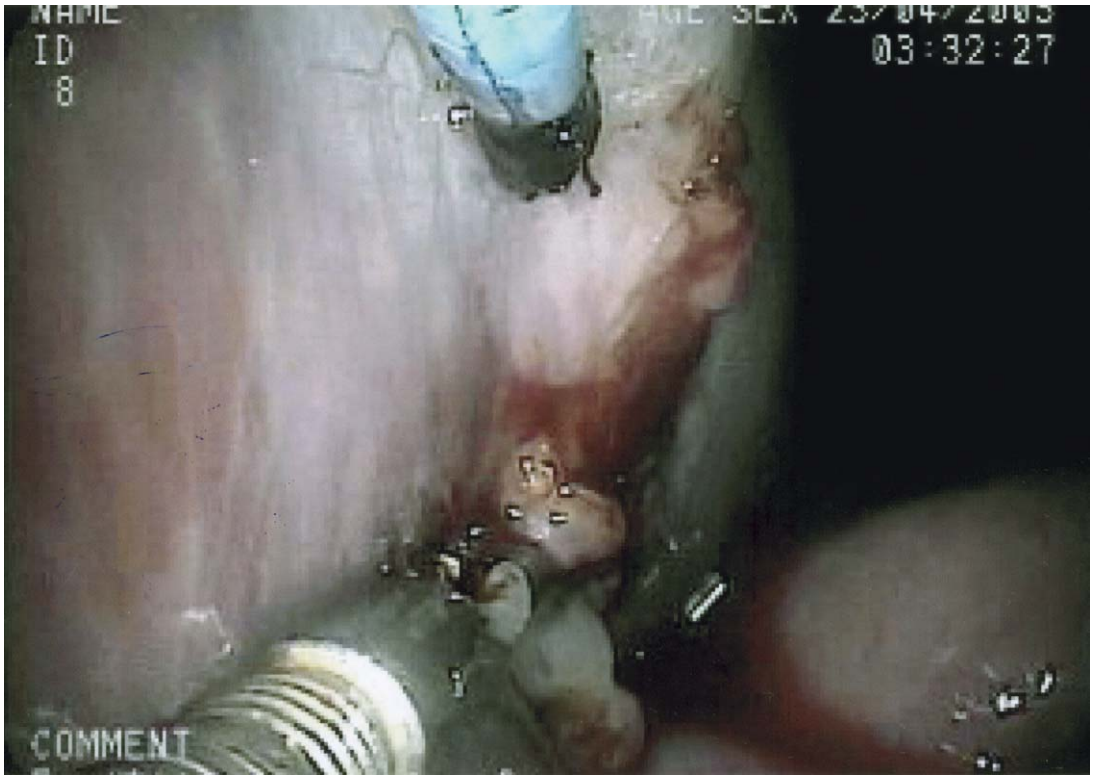

Fig. 4. The gallbladder is retracted and dissected with a monopolar needle-knife cautery while the liver is held up with the device's shaft.

being described in the literature.[7,8] Most recently, the concept of transgastric flexible endoscopic surgeries fired the imagination of surgical endoscopists and advanced gastroenterologists.[9] These techniques are more than just theoretical as evidenced by reports of laboratory experiments such as this one and even of early clinical applications.[10–14] Anecdotal reports are surfacing worldwide of small series of transgastric tubal ligations, staging peritonoscopy, and even cholecystectomy. At meetings of gastrointestinal societies during the past year, presentations of videos by pioneers such as Drs. Rao and Reddy of India showing human transgastric procedures have generated much discussion ranging from excitement to approbation. The growing interest of these efforts is evidenced by the number of abstracts presented at Digestive Disease Week. In 2003, there were no abstracts dealing with transgastric endoscopy, whereas in 2004 there were three, and this year, six addressed this subject.

The appeal of transgastric FES may not be immediately apparent, considering the more-or-less mainstream acceptance of laparoscopic surgery in particular. On the other hand, FES represents a natural evolution in video-technology and theoretically offers patient benefits: less pain, better cosmetic results, and lower physiologic stress. Perhaps most important will be the public perception of this new approach. Much like what happened with laparoscopic cholecystectomy, public demand, either because it is "incisionless" or simply because it is the newest technique, will probably drive adoption.

In an effort to explore the potential of this concept, the authors teamed up with industry to develop tools to facilitate transgastric FES. Taking a theoretical position that transgastric FES was a future probability, our group developed a consensus regarding the types of instruments and steps of the procedure that would be required to effectively and safely perform such procedures. Our experience in the laboratory to date indicates both the possibilities and the difficulties of this novel approach. Insertion of the FES devices was easily accomplished, as was safe advancement into the abdominal cavity. Manipulations in the lower abdomen were quite easy, and it was clear that procedures such as appendectomy, oophorectomy, peritoneal biopsy, and tubal ligation would be feasible. Of course, these are procedures easily done laparoscopically or open with low morbidity and risk and therefore are less likely to create a driving demand for a transgastric approach.

Potentially of more interest are procedures of the upper abdomen such as cholecystectomy, hiatal hernia repair, obesity surgery, or staging procedures that require node or wedge liver biopsy. In our laboratory experience, these procedures represented more of a technical challenge to accomplish, partly because they involved operating in the disorienting retroflexed position but primarily because of the need to operate and provide retraction with a single instrument. The ability of our devices to be manipulated into position and then "frozen" in place, while still allowing full mobility of the tip, proved key. The device could be manipulated into place beneath the liver or spleen and then locked into place. The organs would then be draped onto the shaft of the stiffened instrument and could be displaced anteriorly. The tip remained mobile and allowed surgical dissection in the resulting small field. Because of the thin multilobulated nature of the pig's liver and spleen, this maneuver proved to be somewhat difficult and we subsequently switched to a dog model as it had a more user-friendly anatomy. Despite this, we had only limited success in hiatal exposure (50%), although subsequent trials in human cadavers have been more encouraging. While the gallbladder could be routinely exposed with these maneuvers, removing the gallbladder proved difficult. The primary problem was achieving fine control of the dissecting tool, a standard endoscopic needle-knife cautery. Current hand controls of the prototype devices did not allow smooth, controlled movements of this very aggressive tool. The complexity of the multifunctional handle also played a role as the surgeon had multiple controls and devices to move at the same time. Perforations or inadvertent lacerations of the cystic artery resulted and forced abandonment of two of the cholecystectomy attempts. Future development of the instruments and their controls will need to be made as well as better energy sources such as bipolar endoscopic graspers or ultrasonic coagulating shears.

The final and perhaps greatest hurdle between our studies and eventual human clinical use is closure of the gastric exit site. The gastrotomy represents a new source of potential complication and, as such, problems must be extremely rare or they will offset any advantage gained by the FES transgastric approach. There are currently several endoscopic suturing devices either available or in development and this study tried several of them. While most were able to close the small gastrotomy, they seemed to fail the test of consistent dependability that would be needed for human use. Further development of a closure device or method is imperative.

There are other concerns that have been raised during discussions of transgastric laparoscopy such as patient indications and contraindications, risk/benefit analysis, complication management, and, perhaps most significant, training and credentialing

Table 4. Results of transgastric laboratory experience

Procedure	No. Attempted	No. Successful	Percent	Time (range) (min)
Esophageal insertion/ gastric positioning	10	10	100	4 (2–12)
Gastrotomy and abdominal insertion	10	10	100	5 (3–8)
Cecal retraction	10	10	100	3 (2–4)
Run small bowel	10	10	100	11 (3–16)
Liver explore/ biopsy	10	9	90	7 (4–13)
Hiatal exposure	10	5	50	9 (7–22)
Cholecystectomy	3	1	33.3	31

issues. While this study did not specifically deal with these topics, they remain issues that will need to be addressed before widespread adoption of this novel approach.

CONCLUSION

There is a growing consensus among gastrointestinal physicians and surgeons that flexible endoscopy is poised to become a major new tool for the performance of gastrointestinal surgery. Early reports of procedures such as transgastric appendectomy and cholecystectomy are encouraging but widespread adoption of "incisionless" surgery will require major improvements in current flexible endoscopes and development of new instrumentation. We present the preliminary results of a development program pairing gastrointestinal surgeons and gastroenterologists with medical device engineers to create devices designed to accomplish transluminal FES.

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Discussion

Dr. Brian Dunkin (Miami, FL): Flexible endoscopic surgery is in its infancy, but it is an exciting new frontier in minimally invasive surgery that is re-energizing the surgical world's interest in endoscopy. The authors of this paper are a veritable Who's Who list of innovators in minimally invasive surgery and flexible endoscopy, and this effort is an example of how collaboration between gastroenterology and surgery can be extremely productive.

The paper represents a deceptively large amount of work. The authors had to define a goal, and in this case that was to replicate appendectomy, cholecystectomy, and diagnostic laparoscopy using this transgastric approach; define the steps necessary to do that; identify the problems encountered in each step; and then devise novel instrumentation to address those problems. After that, they had to go ahead and test it. So it is a large body of work represented in one manuscript.

For anyone who has tried this, there are multiple hurdles encountered in transgastric flexible endoscopic surgery. In the upper abdomen in particular,

the instruments are in a retroflexed position, causing paradoxical motion and making orientation difficult. Retraction is necessary to gain exposure, but standard endoscopes are inadequate, with only single working channels and no triangulation of the image. Innovative platforms such as these are necessary, and this articulating flexible endoscopic guide is a significant step toward solving many of these problems. Now, if we could just figure out a way to securely close that gastrotomy.

I have two questions, in closing, for Dr. Swanstrom. First, were there any problems encountered in orientation working in this retroflexed position and looking back up at the gallbladder? And second, how many personnel were required for the cholecystectomy procedure, and what was their training?

Dr. Swanstrom: Thank you, Dr. Dunkin, first of all for agreeing to review the manuscript, which I appreciate and for your questions, which were very perceptive.

With the current generation of instrumentation, there are three large 5.5-mm channels, including the scope, and we maintain visual orientation by traditional torquing of this scope. So when we retroflex the device to work in the upper abdomen, obviously the image would go upside down, which is quite disorienting. When we torque the scope like you would in a standard flexible endoscopy, it rotates in the channel and rights the image. It is a very important point. Early on, we looked at a specifically designed new operating endoscope and found that the radical maneuvers required for intrabdominal surgery were extremely disorientating, because you were essentially operating upside down or at other disadvantaged angles. So we found this scope within a device to be more user friendly.

To answer your other question, how many people does this take; right now it takes quite a few. There were essentially two technicians or endoscopic nurses, one to run each of the graspers, a device mounted to the operating table that held the scope, and then I was manipulating the scope controls and running graspers in and out of the channel at the same time. It is definitely something that requires some work. We are looking at designing different scope holders or other ways of positioning things to decrease the personnel needs. For example, right now it takes three people to do a cholecystectomy. So you definitely lose a little advantage there.

Thank you.

Virally Directed Fluorescent Imaging Improves Diagnostic Sensitivity in the Detection of Minimal Residual Disease After Potentially Curative Cytoreductive Surgery

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Completeness of cytoreduction is an independent prognostic factor after cure-intended surgery for peritoneal carcinomatosis. NV1066, a genetically engineered herpes simplex virus carrying the transgene for green fluorescent protein, selectively infects cancer cells. We sought to determine the feasibility of virally directed fluorescent imaging in the intraoperative detection of minimal residual disease after cytoreductive surgery. NV1066 infected human gastric cancer cells, OCUM-2MD3, and mesothelioma JMN cells at all doses. The infected cells expressed green fluorescent protein and were killed. OCUM-2MD3, and mesothelioma JMN cells at all doses. Peritoneal carcinomatosis was established in mice by injection of OCUM cells into the peritoneal cavity. Forty-eight hours after intraperitoneal injection of NV1066, two experienced surgeons resected all visible disease and identified mice free of disease. Eight of 13 mice thought to be free of disease were found to have residual disease as identified by green fluorescence (mean number of observations: 5; range: 1–9). Residual disease was most frequently observed in the retroperitoneum, pelvis, peritoneal surface, and liver. Specificity of NV1066 infection to tumor nodules was confirmed by immunohistochemistry and by polymerase chain reaction for viral gene. Virally directed fluorescent imaging, a novel molecular imaging technology, can be used for real-time visualization of minimal residual disease after cytoreductive surgery and can improve the completeness of cure-intended resection. (J GASTROINTEST SURG 2005;9:1138–1147) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Herpes simplex virus, oncolytic viral therapy, peritoneal carcinomatosis, peritonectomy, gene therapy

The prognosis for patients with peritoneal carcinomatosis (PC) from gastrointestinal malignancies is dismal. Recent efforts combining aggressive cytoreduction of intraperitoneal disease with perioperative chemotherapy have demonstrated improved overall survival and quality of life in these patients.[1,2] Among the most important prognostic factors determining survival after cytoreduction is completeness of resection. Unfortunately, the ability to identify macroscopic or microscopic residual tumor deposits at the time of cytoreductive surgery is limited, and, as such, disease recurs in the majority of patients. Methods that enhance intraoperative detection of minimal residual disease may improve completeness of cytoreduction and patient outcomes.[3]

Oncolytic herpes viruses are replication-competent, attenuated type 1 herpes simplex viruses (HSV-1) that selectively infect cancer cells, sparing

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normal cells. Their therapeutic efficacy in experimental models of gastrointestinal cancer has been demonstrated in previous publications.[4,5] One such virus is NV1066, a genetically engineered oncolytic HSV strain that carries the transgene for marker protein, enhanced green fluorescent protein (GFP). Cancer cells infected with NV1066 constitutively express GFP, which can be detected using fluorescent imaging. Advantages of such a marker protein have been demonstrated in several in vitro experiments. The recent development in our laboratory of a fluorescent laparoscopic system, in combination with the advent of NV1066, has led to the discovery of novel applications of in vivo cancer imaging.

We evaluated the ability of NV1066-mediated cancer cell-specific expression of GFP to enhance the intraoperative detection of minimal residual disease after cytoreductive surgery using virally directed fluorescent imaging (VFI).

MATERIALS AND METHODS

Cells

The human gastric cancer cell line OCUM-2MD3 and the malignant mesothelioma cell line JMN were studied. OCUM-2MD3 cells were a gift from Dr. Masakazu Yashiro (Osaka City University Medical School, Osaka, Japan) and were grown in Dulbecco's modified Eagle's medium supplemented with high glucose, 2 mmol/L L-glutamine, 0.5 mmol/L sodium pyruvate, 100 U/mL penicillin, 100 mg/mL streptomycin, and 10% fetal calf serum (FCS). JMN cells were a gift of Dr. Francis Sirotnak (Memorial Sloan-Kettering Cancer Center, New York, NY) and were grown in Roswell Park Memorial Institute 1640 media supplemented with 100 U/mL penicillin, 100 mg/mL streptomycin, and 10% FCS. Vero cells (American Type Culture Collection, Rockville, MD) were grown in minimum essential medium supplemented with 100 U/mL penicillin, 100 mg/mL streptomycin, and 10% FCS. Cells were maintained in a 5% CO_2 humidified incubator at 37°C.

Virus

NV1066 is a replication-competent oncolytic HSV-1 strain whose construction has been described in detail.[6] Briefly, NV1066 was derived from the wild-type HSV-1 virus (F strain) by deletions in the viral virulence genes ICP0, ICP4, and $\gamma_1$34.5. These deletions attenuate the virus conferring selectivity for infection of cancer cells and render the virus safe for use in humans. In addition, the transgene for enhanced GFP was inserted into the deleted region under the control of a constitutively expressed cytomegalovirus promoter. Viral stocks were propagated on Vero cells and titered by standard plaque assay.

Detection of Green Fluorescent Protein Expression by Fluorescent Microscopy

Monolayer cultures of OCUM-2MD3 cells were incubated at 37°C and infected with NV1066 at a multiplicity of infection (MOI, ratio of the number of viral particles to the number of tumor cells) of 1.0. A Zeiss LSM 510 confocal laser scanning microscope (Carl Zeiss, Inc., Oberkochen, Germany) and the MetaMorph Imaging System (Downingtown, PA) were used to visualize GFP-expressing cancer cells hourly after infection. GFP expression was identified after placement of specific excitation and emission filters to detect GFP. The Retiga EX digital CCD camera (Qimaging, Burnaby, Canada) was used for image capture.

Detection of Green Fluorescent Protein Expression by Flow Cytometry

Cultured cells (5×10^4) were plated in six-well flat-bottom assay plates (Becton Dickinson, Franklin Lakes, NJ) in 2 mL of media. After overnight incubation at 37°C, cells were infected with NV1066 at MOIs of 0.01, 0.1, or 1.0 in 100 μL of phosphate-buffered saline (PBS). Untreated cells served as a negative control. Daily after infection, cells were harvested with 0.25% trypsin in 0.02% EDTA, combined with the supernatant fraction, centrifuged, washed with PBS, and resuspended in 100 μL of PBS; 5 μL of 7-amino-actinomycin (7-AAD; BD Pharmingen, San Diego, CA) was added as an exclusion dye for cell viability. Data for GFP expression from 1×10^4 cells were acquired on a FACS Calibur unit equipped with Cell Quest software (Becton Dickinson, San Jose, CA). Results are reported as the percentage of live cells expressing GFP. In addition, GFP-positive cells were sorted using the MoFlo High-Performance Cell Sorter (DakoCytomation, Carpinteria, CA) and stained with rabbit anti–HSV-1 polyclonal antibody (Biogenex, San Ramon, CA) to confirm viral infection of green cells. A biotinylated secondary antibody was added and visualized with streptavidin-labeled horseradish peroxidase and chromogen solutions. Each experiment was repeated a minimum of three times.

Cytotoxicity Assay

Cytotoxicity assays were performed by plating 2×10^4 cells in 24-well plates in 1 mL of media.

After overnight incubation at 37°C, cells were infected with NV1066 diluted in 100 μL media at MOIs of 0.01, 0.1, and 1.0. On days 3 to 7 after infection, cells were lysed with 1.35% Triton-X solution to release intracellular lactate dehydrogenase (LDH). LDH was then quantified with a Cytotox 96 nonradioactive cytotoxicity assay (Promega, Madison, WI) that measures the conversion of a tetrazolium salt into a red formazan product. Absorbance was measured at 450 nm with a microplate reader (EL321e, Bio-Tek Instruments, Winooski, VT). Results are expressed as the surviving percentage of cells as determined by the measured absorbance of each sample relative to control, untreated cells. All samples were tested, and experiments were replicated, in triplicate.

Animal Model of Peritoneal Carcinomatosis

All animal procedures were performed under the guidelines approved by the Memorial Sloan-Kettering Institutional Animal Care and Use Committee. Eight- to 10-week-old athymic mice (National Cancer Institute, Bethesda, MD) were housed in a temperature- and light-controlled animal facility. Food and water were permitted ad libitum. Animals were anesthetized with inhalational methoxyflurane for all experimental manipulations and were sacrificed by CO_2 inhalation at the termination of the experiment.

PC was established by injection of 1×10^7 OCUM-2MD3 cells suspended in 500 μL PBS into the peritoneal cavity of athymic mice (n = 24). Twenty-one days after implantation of tumor cells, animals were treated with a single intraperitoneal injection of 1×10^7 plaque-forming units (PFU) of NV1066 in 100 μL of PBS (n = 21). Three animals with PC were treated with an intraperitoneal injection of 100 μL of PBS, and three additional animals without PC were treated with a single intraperitoneal injection of 1×10^7 PFU of NV1066 to serve as negative controls. Forty-eight hours after viral administration, laparotomy was performed on all animals by two experienced surgeons with the intent to resect all intra-abdominal disease. Partial or complete resection of organs was performed if deemed necessary to achieve complete resection.

In Vivo Fluorescent Imaging

Immediately after resection, the peritoneal cavities of all animals were systematically examined by both bright-field and fluorescent laparoscopy. We use a laparoscopic system, developed in concert with Olympus America, Inc. (Scientific Equipment Division, Melville, NY), that images in both bright-field and fluorescent modes permitting the detection of GFP. The light source is derived from the Olympus Visera CLV-U40 model (Olympus America, Inc., Melville, NY) adapted with an interchangeable excitation filter set at 470 ± 20 nm to accommodate the minor excitation peak of GFP at 475 nm and an emission filter fixed at 500 nm to accommodate the emission peak of GFP at 509 nm. The camera processor was an Olympus Visera OTV-S7V with an emission filter set at 510 nm.[6] A control button incorporated directly into the camera head enables rapid exchange between bright-field and fluorescent modes. GFP images were taken with minimal background illumination to illustrate the surrounding organs.

With this system, each mouse was individually and systematically examined by five independent, blinded observers. Each observer examined 12 predetermined anatomic areas (liver, right subdiaphragm, stomach, spleen, left subdiaphragm, intestine, mesentery, retroperitoneum, left kidney, right kidney, pelvis, and peritoneal surface) in a systematic fashion for the presence of residual disease as determined by the presence or absence of green fluorescence. These anatomic areas were designed on the peritoneal cancer index developed by Sugarbaker.[7] Investigators recorded the presence ("Yes") or absence ("No") of green fluorescence on a data sheet. Animals and data sheets were matched and coded with random numbers known only to a single investigator who was neither a surgeon nor an observer. Animals in which grossly evident disease remained after resection were excluded from the study. This experiment was repeated twice. Animals with disease treated by PBS and animals without disease treated by NV1066 (negative controls) were also observed in a similar fashion as described above.

Histologic Confirmation of Residual Microscopic Disease

After complete examination of each animal by all observers, intra-abdominal tissue biopsies (areas that were both green and not green) were fixed in 10% phosphate-buffered formalin and embedded in paraffin for histologic analysis. Serial 8-μm sections of all tissue blocks were cut and stained with hematoxylin-eosin (H&E) to assess for the presence of tumor. Additional slides were stained with rabbit anti–HSV-1 polyclonal antibody (Ready-to-Use, Biogenex) to detect the presence of virus in harvested tissues. A biotinylated secondary antibody was added and visualized with streptavidin-labeled horseradish peroxidase and chromogen solutions (Super Sensitive Ready-to-Use Detection System, Biogenex).

Counterstaining with Harris hematoxylin was performed.

Confirmation of Viral Specificity to Residual Microscopic Disease by Real-Time Polymerase Chain Reaction

Additional random intra-abdominal tissue samples were harvested and snap-frozen in liquid nitrogen. Genomic DNA was isolated using standard protocols (Wizard Genomic DNA Isolation Kit, Promega). Real-time quantitative polymerase chain reaction (PCR) was performed using an ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Forward (5′-ATGT TTCCCGTCTGGTCCAC-3′) and reverse (5′-C CCTGTCGCCTTACGTGAA-3′) primers and a dual-labeled fluorescent TaqMan probe (5′-FAM-CCCCGTCTCCATGTCCAGGATGG-TAMRA-3′) were designed to amplify and detect the 111-base pair fragment of the HSV immediate-early gene ICP0. Forward (5′-CGCCTACCACATCCA AGGAA-3′) and reverse (5′-GCTGGAAT TACCGCGGCT-3′) primers and a dual-labeled fluorescent TaqMan probe (5′-VIC-TGCTGGCA CCAGCTTGCCCTC-TAMRA-3′) were also designed for the 87-base pair coding sequence of 18s rRNA to normalize to the amount of total DNA present. The PCR conditions were as follows: stage 1, 50°C for 2 minutes; stage 2, 95°C for 10 minutes; stage 3 (35 cycles), 95°C for 15 seconds and 60°C for 1 minute; and stage 4, 25°C soak.

RESULTS

NV1066 Infects Cancer Cells, Expresses Green Fluorescent Protein, and Kills Cancer Cells

In vitro, NV1066 infected cancer cells, expressed GFP, and was cytotoxic to both cell lines at all MOIs (Fig. 1). Flow cytometry for GFP was performed to demonstrate infectivity and expression of GFP in NV1066-treated OCUM-2MD3 and JMN cells

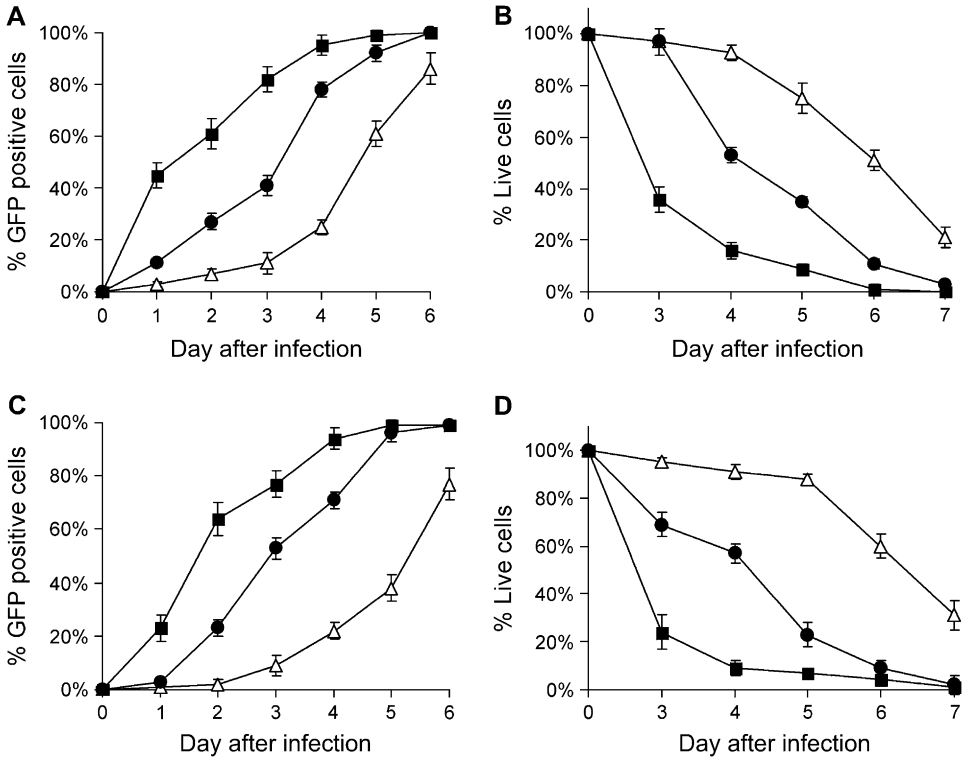

Fig. 1. NV1066 infects cancer cells, expresses GFP, and kills cancer cells. Monolayer cultures of OCUM-2MD3 human gastric cancer cells and JMN human malignant mesothelioma were incubated at 37°C and infected with NV1066 at an MOI of 0.01 (*open triangle*), 0.1 (*circle*), and 1.0 (*square*). Cells were harvested daily after infection and analyzed by flow cytometry for GFP expression or LDH cytotoxicity assay to determine cell kill. (**A**) Expression of GFP after infection of OCUM-2MD3 cells is plotted as percentage of live cells expressing GFP. (**B**) Cytotoxicity of OCUM-2MD3 cells after infection is plotted as percentage of live cells remaining compared with untreated control cells. (**C, D**) Similar results are observed with JMN cells. GFP = green fluorescent protein; MOI = multiplicity of infection, ration of viral particles to tumor cells.

(Fig. 1, *A*,*C*). Six days after infection of OCUM-2MD3 cells at MOIs of 0.1 and 1.0, 100% (±0%) of cells expressed GFP ($P < .01$) (Fig. 1, *A*). Even at a low MOI of 0.01, 86% (±3%) of cells expressed GFP 6 days after infection ($P < .01$). Similar results were obtained with JMN cells (Fig. 1, *C*).

To examine the oncolytic efficacy of NV1066, dose-dependent cytotoxicity assays were performed against OCUM-2MD3 and JMN cells (Fig. 1, *B*,*D*). NV1066 demonstrated dose-dependent cytotoxicity against both cell lines. Seven days after infection of OCUM-2MD3 cells at an MOI of 1.0, 100% (±1%) of cells were killed ($P < .01$) (Fig. 1, *B*). At 10-fold lower MOIs of 0.1 and 0.01, 97% (±1%) and 79% (±4%) of cells were killed 7 days after infection, respectively ($P < .01$). Similar results were seen with JMN cells (Fig. 1, *D*).

Green Fluorescent Protein Can Be Detected in Infected Cancer Cells Within Hours of Infection

The GFP signal was detected as early as 4 to 6 hours after infection (Fig. 2, *A*). The GFP signal intensity of infected cells was significantly higher than the autofluorescence of normal cells (230–670 logs). Immunohistochemistry for herpes viral antigen confirms the localization of GFP in HSV-infected cancer cells (Fig. 2, *B*,*C*). All of the green cells that were sorted by flow sorter were stained by HSV-1 antibody, confirming that the green fluorescence is indeed caused by NV1066 infection. Similarly, non-green cells were not stained with HSV-1 antibody.

NV1066-Mediated GFP Expression Enables the Detection of Minimal Residual Disease After Complete Resection

In vivo, macroscopically undetectable tumor nodules by gross inspection and bright-field laparoscopy were readily identified by fluorescent laparoscopy because of green fluorescence. Representative images are shown in Fig. 3.

Eight animals in which grossly evident disease remained after resection were excluded from the study. In the remaining animals, a maximum of 780 observations were possible (13 mice × 12 anatomic sites × 5 observers). Only 757 observations were recorded, however, because completely resected organs were excluded from the analysis. Residual tumor, as identified by green fluorescence during laparoscopy, was detected in 8 of 13 mice. The mean number of green observations per animal for these eight mice was 5.25 (range, 1–9). Table 1 shows the number of green observations for each of the 12 anatomic sites, aggregated over all mice and observers. Minimal residual disease as identified by green fluorescence was most frequently observed in the retroperitoneum, pelvis, peritoneal surface, and liver. Minimal residual disease was least commonly observed in the mesentery, stomach, and spleen. No areas of green fluorescence were identified in the negative control animals. Analysis of interobserver agreement among the five observers revealed agreement in 99% of observations.

Confirmation of Residual Microscopic Disease

Biopsies of tissues that were identified as green during fluorescent laparoscopy were confirmed to harbor tumor by routine H&E histologic analysis. Furthermore, immunohistochemical staining for herpes viral antigen demonstrated that NV1066 localized to tumor deposits in a highly specific manner. No tumor or virus was detected in non-green tissue biopsies that were analyzed. Representative sections are shown in Fig. 4. PCR amplification of the viral gene ICP0 was used to further confirm the absence of NV1066 in non–tumor-bearing (non-green) tissues. ICP0 was not detected in any normal tissue

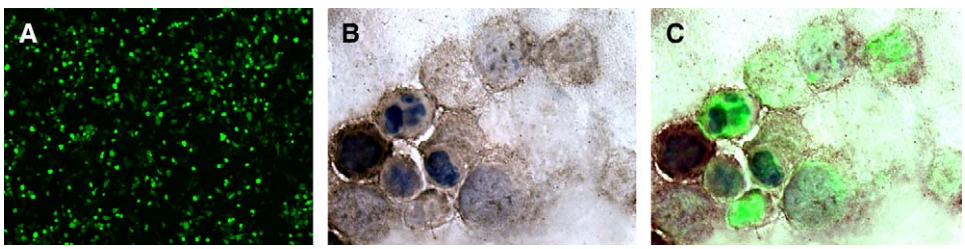

Fig. 2. GFP can be detected within infected cancer cells within hours of infection. Monolayer cultures of OCUM-2MD3 human gastric cancer cells were infected with NV1066 at an MOI of 1.0. (**A**) Within 4 to 6 hours of infection, GFP is detected by fluorescent microscopy (magnification 10×). (**B**) Immunohistochemical staining for herpes viral antigen demonstrates the presence of intracellular herpes viral antigen (magnification 40×). (**C**) Digital fluorescent overlay demonstrates production of GFP in herpes virus-infected cells (magnification 40×). MOI, multiplicity of infection, ratio of viral particles to tumor cells; GFP = green fluorescent protein.

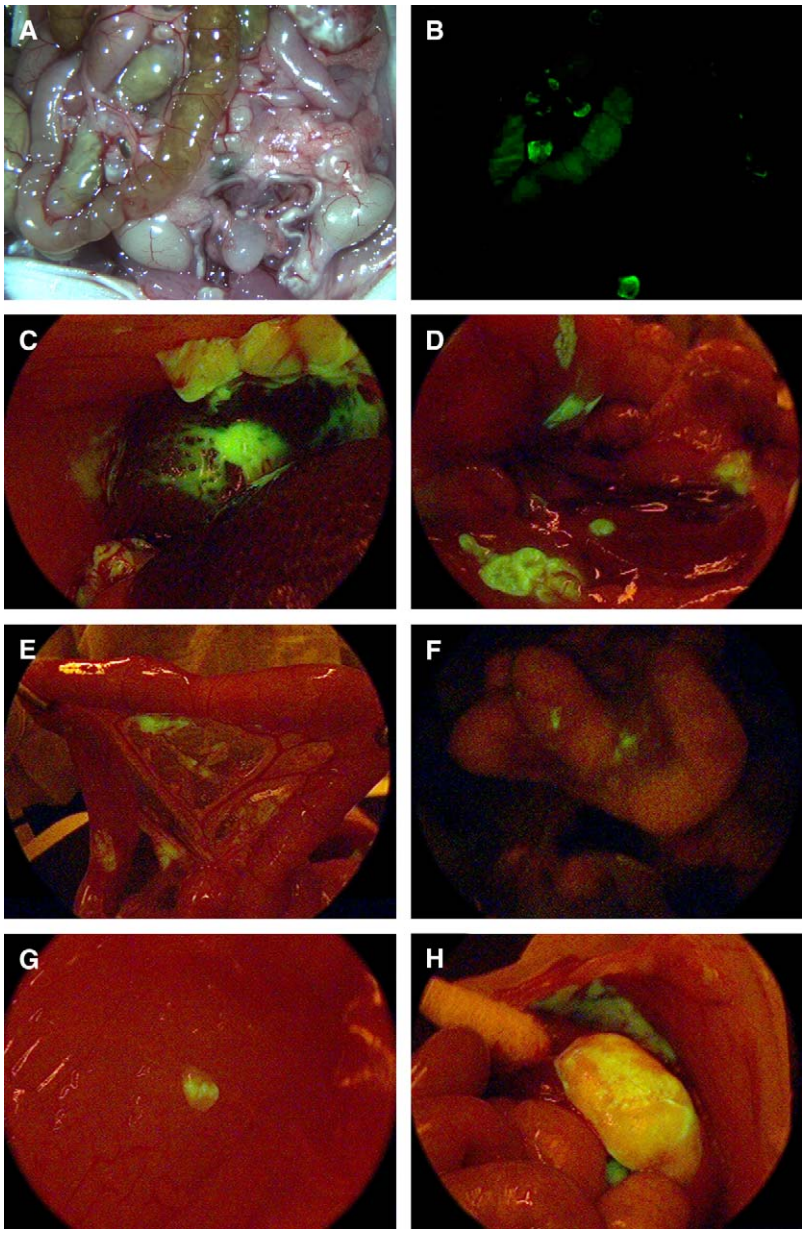

Fig. 3. NV1066-mediated GFP expression enables the detection of minimal residual disease after complete resection. A murine model of peritoneal carcinomatosis (PC) was established by injection of 1×10^7 OCUM-2MD3 cells into the peritoneal cavity of athymic mice. Twenty-one days later, animals were treated with a single intraperitoneal injection of 1×10^7 PFU of NV1066. Forty-eight hours after viral administration, laparotomy with complete cytoreduction was performed. The peritoneal cavities of all animals were then systematically examined by both bright-field and fluorescent laparoscopy for the detection of residual disease. Overlay images are created by digital superimposition of the fluorescent image over the bright-field image. Representative images are shown. (**A, B**) Residual subdiaphragmatic and subhepatic tumor, respectively, that were not detected by bright-field examination. (**C, D**) Mesenteric and small intestinal serosal tumor deposits that were not identified by routine bright-field laparoscopy. (**E**) A 1-mm tumor deposit on the peritoneal surface that was missed by all five observers using bright-field laparoscopy but identified by all five observers using fluorescent laparoscopy. (**F**) Residual pelvic disease that was only identified by fluorescent laparoscopy. (**G**) A 1-mm tumor deposit on the peritoneal surface that was missed by all five observers using bright-field laparoscopy but identified by all five observers with fluorescent laparoscopy. (**H**) Residual pelvic disease that was only identified by fluorescent laparoscopy. PFU = plaque forming units.

Table 1. Frequency of enhanced identification of minimal residual disease by green fluorescence at each of 12 anatomic sites

Anatomic site	Number of bright-field observations	Number of times minimal residual disease was identified by green fluorescence*	Percentage (%)†
Retroperitoneum	65	35	54
Pelvis	65	34	52
Peritoneal surface	65	25	38
Liver	65	25	38
Left subdiaphragmatic	55	20	36
Intestine	45	15	33
Left kidney	60	15	25
Right kidney	65	15	23
Right subdiaphragmatic	50	10	20
Mesentery	40	6	15
Stomach	40	5	13
Spleen	40	5	13

*Data are aggregated over all mice and observers.
†Percentages are calculated as the number of green observations per total number of observations at each anatomic site. The following sites were missing both bright-field and green fluorescence observations as the organs underwent near-complete resection because of macroscopic disease (left subdiaphragm [10], intestine [20], left kidney [5], right subdiaphragmatic [15], mesentery [25], stomach [25], and spleen [25]).

biopsy that was analyzed, confirming the high specificity for viral infection of cancer cells, sparing normal cells (data not shown).

DISCUSSION

Peritoneal surface involvement occurs in as many as 20% to 30% of patients with gastric, colon, appendiceal, and pancreatic cancers.[8] Median survival in these patients with peritoneal disease is usually less than 1 year.[9] Moreover, recurrent bowel obstructions, malignant ascites, fistulization, and pain result in diminished quality of life.

Aggressive loco-regional treatment of these patients combining cytoreductive surgery with perioperative intraperitoneal chemotherapy aims to improve patient survival and quality of life.[8,9] Cytoreduction entails resection of all visible tumor and stripping of all peritoneal surfaces that contain metastatic nodules. Visceral peritoneal involvement often requires concomitant resection of intra-abdominal organs including the stomach, small intestine, and colorectum. In addition, perioperative intraperitoneal chemotherapy is administered to sterilize residual microscopic disease.

Such aggressive loco-regional treatment has resulted in improved survival and quality of life as reported in several publications. In one such study, Verwaal et al.[3] randomized 117 patients with PC caused by colorectal cancer to receive either standard systemic chemotherapy with or without palliative surgery, or aggressive cytoreduction combined with hyperthermic intraperitoneal chemotherapy.[3] Their reported 5-year survival of 19% exceeded historical controls, whose 5-year survival approached 0%. Similar favorable results using this approach have also been reported in patients with carcinomatosis secondary to gastric cancer, pseudomyxoma peritonei, and nongastrointestinal malignancies including peritoneal mesothelioma and sarcomatosis.[8,10,11]

Among the most important prognostic factors after cytoreduction is completeness of resection. In the series by Verwaal et al.,[3] the median survival in a subgroup of patients in whom complete cytoreduction was achieved was 42.9 months, compared with 17.4 months in patients with minimal residual disease, defined as residual macroscopic tumor $\leqslant$ 2.5 mm after cytoreduction.[3] Similarly, the *completeness of cytoreduction score* developed by Sugarbaker,[7] an assessment made by the operating surgeon of the extent of residual disease after cytoreduction, has been shown to be a major prognostic indicator in patients with peritoneal surface malignancies.

The ability to detect small macroscopic residual peritoneal disease is largely limited by the lack of contrast difference between tumor nodules and surrounding normal tissues. Moreover, microscopic nodules are beyond the limits of detection of the unaided eye. Technology improving the intraoperative detection of residual peritoneal disease would facilitate complete cytoreduction and improve survival in these patients.

We demonstrate that VFI using NV1066-mediated tumor cell-specific production of GFP enhances the detection of minimal residual disease after cytoreduction in a murine model of PC. The green

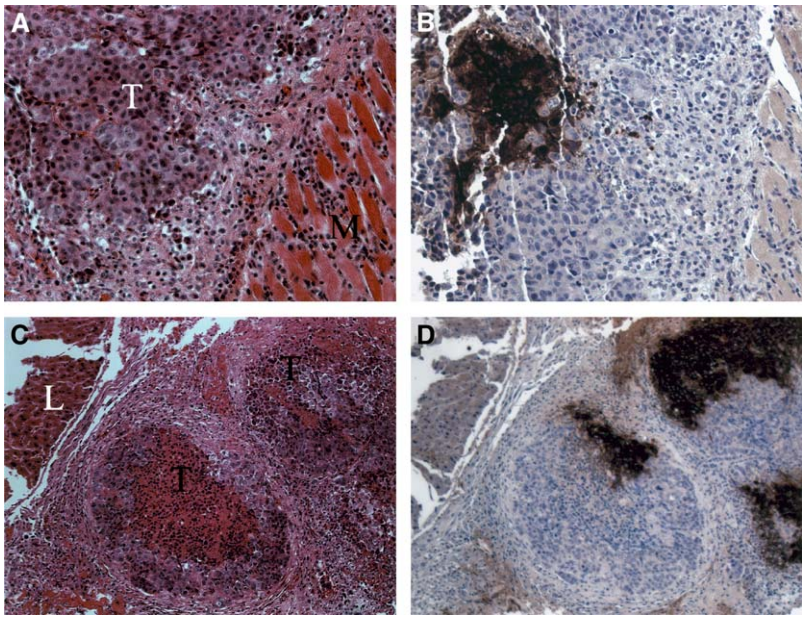

Fig. 4. Histologic confirmation of residual microscopic metastatic disease. Intra-abdominal tissue biopsies were harvested, fixed in formalin, and embedded in paraffin. Serial 8-μm sections of tissue blocks were cut and stained with hematoxylin-eosin (H&E) to assess for the presence of tumor. Immunohistochemistry was performed using the herpes simplex virus type 1 (HSV-1) polyclonal antibody to detect for the presence of NV1066. Representative sections are shown. H&E staining demonstrates tumor deposits on the diaphragm that were missed by bright-field laparoscopy but identified by fluorescent laparoscopy (**A**). (**B**) The presence of virus in the tumor is confirmed by immunohistochemistry and further demonstrates the specificity of virus for tumor cells. (**C**) H&E confirms the presence of tumor in a subhepatic deposit that was missed by bright-field laparoscopy. (**D**) Immunohistochemistry confirms the presence of virus in the tumor. Magnification 40× (**A, B**) and 20× (**C, D**). T, tumor; M, muscle of the diaphragm; L, liver.

fluorescence emitted by NV1066 is 230 to 670 logs greater than background autofluorescence, allowing clear discrimination between tumor and normal tissues. The mean fluorescent intensity of enhanced GFP expressed by NV1066 is six-fold greater than nonenhanced GFP, and it matures four times more rapidly, reducing the lag time from infection to detection of green fluorescence. Furthermore, enhanced GFP has specific emission and excitation wavelengths (475/509 nm), eliminating autofluorescent interference. After a single intraperitoneal injection of NV1066 and presumed complete cytoreduction by two experienced surgeons, 8 of 13 mice were found to have at least one site of residual disease using VFI. In our study, residual disease was identified most commonly in the retroperitoneum, pelvis, peritoneal surface, and liver. These sites correspond to patterns of recurrence in published human series.[12,13]

In addition to providing a diagnostic benefit, the use of oncolytic herpes viruses in this setting may offer a therapeutic effect. The therapeutic efficacy of NV1066 in a murine model of PC secondary to gastric cancer has already been demonstrated by work in our laboratory.[5] Dose-dependent reduction of peritoneal weights in a murine model of PC was observed after intraperitoneal injection of NV1066. Furthermore, we have also shown that oncolytic herpes viruses interact synergistically when used in combination with chemotherapy.[14] In this study, mice with gastric carcinomatosis treated with combination viral therapy and mitomycin C had reduced tumor burdens compared with either treatment alone.

Finally, the specificity of NV1066 for cancer cells in this study further confirms observations from previous work in our laboratory.[4,15] Immunohistologic and PCR analyses of viral presence after administration confirms specific uptake of virus in tumor tissue, sparing normal tissue. As such, expected toxicity from these agents is minimal, as demonstrated in numerous studies using NV1066 in murine models.[4,5,15] Furthermore, the safety of related oncolytic HSV strains in humans has been established in phase I clinical trials both from our group and others.[16,17]

CONCLUSIONS

Promising survival benefits are being realized for patients with PC from gastrointestinal malignancies following an aggressive multimodal therapeutic approach combining cytoreductive surgery and perioperative chemotherapy. Treatment failure in these patients is frequently the result of unresected minimal residual disease. We demonstrate that VFI using NV1066-mediated tumor cell-specific production of GFP enhances the detection of minimal residual disease after cytoreduction of PC. Furthermore, NV1066 in addition to being diagnostic is therapeutic and can be combined with chemotherapy, an approach recommended in the loco-regional treatment of these patients with advanced disease.

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Discussion

Dr. David Mahvi (Madison, WI): I think this article points out a couple of things. One is that the people best set up to do research on surgical questions are probably surgeons and that this is a perfect surgical issue: It is a clinical problem, they approached it as a surgeon, and came up with nice results.

Gene therapy, which is something I have been interested in, has always had more promises than results. Most of the gene therapy studies have focused on therapeutic applications of gene therapy. This study really looks at the diagnostic use of gene therapy, and it may be that the promise of gene therapy is not in therapeutics but in diagnostics.

Dr. Fong and his group have been interested in this for a long time and have really championed this herpes simplex virus as a vector when other groups

have essentially abandoned it. The technique that they are using brilliantly uses this virus, which can infect cancer cells and then replicate in other cells; this acts as a multiplying effect, thus allowing the detection of small amounts of disease. I have three questions for the authors.

First, this targeting almost seems too good to be true to me. Is it true that this virus selectively picks up just cancer cells with no other cells next to them? If so, this may be the Holy Grail of cancer therapy. We have had a lot of Holy Grails, and I hate to jump on this bandwagon too soon. So do all different types of GI cancers express this or is this unique to this one cancer cell line?

All of the in vivo studies have looked at IP administration of this. Do you have any data looking at intravenous administration of this drug, which would make more sense clinically? It would be a way to pick up disease that isn't just on the surface of the bowel.

And third, you really just presented animal data. This seems, again, almost perfect: You have a vector that will selectively target cancer cells. Does this work in humans? Do you have the possibility to now proceed into human clinical trials?

Again, I enjoyed this very much, and thanks for asking me to discuss it.

Dr. Adusumilli: Thank you Dr. Mahvi for your kind comments and questions. With regard to your first question, about targeting of the virus specifically to cancer, we tested 110 different cancer cell lines, both human and murine, from 16 different primary organs, and this virus is able to infect and express green fluorescent protein in all the cancer cell lines. There is a difference in the sensitivity among different cancer cell lines; some are infected and expressed immediately, and others within 48 to 72 hours. One group in the laboratory is looking at targeting receptors on cancer cells. The HVEM receptors and GD receptors are very well known to be specific for herpes viruses, studied by the virologists for the last 50 years. These receptors are expressed in cancer cells, and this could be one of the reasons for the specificity. More than infection, the virus is able to replicate, exploiting the cellular metabolic rate, which is increased in the cancerous cells and cancer tissue. That may be another reason why the virus is able to survive and replicate selectively in cancer cells. Some researchers were concerned whether this virus will infect and replicate in high replicative cells such as bone marrow cells and the intestinal mucosa, and to date, both from our laboratory and from independent investigators, we did not find any evidence of replication in normal cells.

The second question is related to the route of administration. For this presentation the virus was administered intraperitoneally, and that is how we started initially, intrathoracic and intraperitoneal. In later experiments, we were excited to notice that irrespective of the site of administration, the virus is able to travel both by hematogenous and lymphatic spread and infect specifically the cancer tissue. My colleagues, Karen Hendershott and Yun Shin Chun, both in the laboratory, are currently working on different routes of administration, not only in the cavities by systemic intravenous injection but also in a breast cancer model, injecting in the mammary fat pad and looking at the different metastases in advanced cancer. As of now, apart from intracranial route, we have tested every other route, and this virus is able to target the cancer tissue.

In response to the third question, about the applicability in human beings, as most of you know, the phase I study was completed by Dr. Fong for multiple colorectal metastases in the liver at Memorial. We subsequently went through an FDA audit successfully. The virus is proven to be safe for use in human beings. Currently, a multicenter phase II trial is about to start recruiting patients. We are also excited about pursuing the diagnostic and therapeutic uses of the HSV.

Contrast-Enhanced Intraoperative Ultrasonography During Hepatectomies for Colorectal Cancer Liver Metastases

Guido Torzilli, M.D., Ph.D., Daniele Del Fabbro, M.D., Angela Palmisano, M.D., Matteo Donadon, M.D., Paolo Bianchi, M.D., Massimo Roncalli, M.D., Ph.D., Luca Balzarini, M.D., Marco Montorsi, M.D.

Preliminary reports showed that contrast-enhanced intraoperative ultrasonography (CEIOUS) provides information on primary or metastatic tumors of the liver that is not obtainable with conventional intraoperative ultrasonography (IOUS). This study validates the impact of CEIOUS, focusing on resective surgery for colorectal cancer (CRC) liver metastases. Twenty-four consecutive patients underwent liver resection using IOUS and CEIOUS for CRC liver metastases. CEIOUS was accomplished with intravenous injection of 4.8 mL of sulphur-hexafluoride microbubbles. CEIOUS found lesions missed at preoperative imaging and at IOUS in four patients and confirmed all of the new findings of IOUS in four patients. In addition, CEIOUS helped to define the tumor margins of the main lesion in 29% of patients with CRC liver metastases. No adverse effects were observed in relation with CEIOUS. In conclusion, CEIOUS improves IOUS accuracy with a significant impact on surgical strategy and radicality in patients who undergo surgery for CRC liver metastases. (J GASTROINTEST SURG 2005;9:1148–1154) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Intraoperative ultrasonography; liver metastases; liver tumors, diagnosis; liver tumors, staging; liver tumors, surgery; laparoscopic ultrasonography; contrast-enhanced ultrasound

Intraoperative ultrasonography (IOUS) is still the most accurate diagnostic technique for detecting focal liver lesions (FLLs).[1,2] However, during surgery for colorectal cancer (CRC) liver metastases, IOUS has a sensitivity of only 82%,[3] and as a consequence may miss nodules less than 1 cm in diameter. This is particularly evident in those patients who undergo surgery after chemotherapy. In these patients, liver fore sites have a similar echo pattern as the surrounding liver parenchyma.

Currently, the application of intravenous ultrasound contrast agent during transcutaneous ultrasonography of the liver (CEUS) has been shown to improve ultrasound nodule detection.[4,5] Indeed, the CRC metastatic lesions are not hypervascular, and they remain mainly unenhanced during the 4 to 5 minutes in which the liver is perfused, allowing a panoramic study of the organ.

Following this rationale, we reported in two preliminary studies with small subsets of patients that contrast-enhanced intraoperative ultrasonography (CEIOUS) is feasible and may provide further information on primary or metastatic tumors of the liver that is not obtainable with IOUS.[6,7] With a focus on CRC liver metastases, we carried out a prospective analysis comparing the findings of CEIOUS with those of preoperative imaging and IOUS in a subset of patients who are carriers of this disease.

PATIENTS AND METHODS

Between September 2002 and April 2005, 24 consecutive patients, 12 males and 12 females, underwent liver resection using IOUS and CEIOUS for CRC liver metastases. The mean age of patients

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was 61.7 years (median 62 years; range 36–78 years). The imaging diagnostic workup for FLLs for the enrolled patients included abdominal ultrasonography and contrast-enhanced spiral computed tomography (CT) in all cases; we also performed magnetic resonance imaging in 6 patients, CEUS in 11 patients, 18-FDG-PET in 7 patients, angiography in 1 patient, and fine-needle biopsy in 1 patient.

Twenty of the 24 patients had diffuse steatosis of the liver, 1 patient had chronic hepatitis, and the remaining 3 patients had normal livers; patients with liver steatosis underwent previous systemic chemotherapy.

IOUS was performed in all cases using an Aloka SDD 5500 (Aloka Ltd; Tokyo, Japan). For IOUS, a microconvex probe (7.5–10 MHz frequency) was used. For CEIOUS, a convex 3 to 6 MHz frequency and 1.88 to 3.76 MHz harmonic frequency transducer was used. In all patients, 2.4 mL of sulphur-hexafluoride microbubbles (SonoVue, Bracco Imaging, Milan, Italy) were injected intravenously through a peripheral vein by the anesthesiologist.

IOUS and CEIOUS were performed by the same surgeon (G.T.). Informed consent was obtained from all patients, but no approval was required by the ethics review board of the hospitals involved in this clinical study because the contrast agent is licensed for use in liver imaging in Italy.

The results of preoperative diagnostic workup, IOUS, and CEIOUS were compared with those of histology.

In patients who underwent operation for CRC liver metastases, the technique was used for detecting new lesions, and every new nodule at CEIOUS was removed if technically resectable. Any new lesions detected at IOUS not confirmed at CEIOUS were also considered as new findings at CEIOUS compared with IOUS.

Statistical Analysis

Sensitivity, specificity, and positive and negative predictive values were calculated for preoperative diagnostic imaging, IOUS, and CEIOUS.

RESULTS

Preoperatively, 45 lesions were detected (mean 1.9; median 1; range 1–6) with a mean tumor diameter of 4.4 cm (median 4; range 2.1–6.6). At IOUS, 54 lesions were detected (mean 2.2; median 1; range 1–6).

CEIOUS was performed with 1 injection per patient, and no adverse effects were observed.[8]

IOUS provided new findings in 5 of 24 patients (21%). CEIOUS demonstrated new nodules in three patients (13%), with no additional fore sites at IOUS; demonstrated new nodules in two patients (8%), in addition to those new lesions detected at IOUS; and confirmed findings of IOUS in four patients (17%) (Table 1). All of these patients had diffuse liver steatosis.

The diameter of the eight new lesions detected only by CEIOUS ranged from 0.2 to 1.1 cm. The lesion detected on magnetic resonance imaging, but not confirmed by IOUS, was not evident at CEIOUS. On histology, all of these nodules proved to be metastases, and the patient with an FLL evident on magnetic resonance imaging, but not confirmed by IOUS and CEIOUS, had no sign of remnant disease at CT performed after 6 months of follow-up.

All of the ten new nodules detected at IOUS and the eight adjunctive nodules detected at CEIOUS were removed and proved to be metastatic lesions at histology.

The sensitivity, specificity, and positive and negative predictive values of preoperative diagnostic imaging, IOUS, and CEIOUS are shown in Table 2.

With a mean follow-up of 15 months (median 15 months; range 6–27 months), just one patient (4%) showed a new lesion in another segment at

Table 1. Comparison in the number of new lesions detected at intraoperative ultrasonography and contrast-enhanced intraoperative ultrasonography in patients with colorectal cancer liver metastases that were modified by intraoperative ultrasonography and/or contrast-enhanced intraoperative ultrasonography as the preoperative staging

	Number of CRC liver metastatic nodules				
Patient	Preoperative imaging	IOUS	CEIOUS	IOUS vs. preoperative imaging	CEIOUS vs. IOUS
1	1	1	2	0	**+1**
2	6	6	9	0	**+3**
3	2	4	4	+2	0
4	3	3	4	0	**+1**
5	2	6	6	+4	0
6	1	3	3	+2	0
7	3	5	6	+2	**+1**
8	2	1	1	−1	0
9	1	1	3	0	**+2**
	21	**30**	**38**	**+10**	**+8**

Bold characters in CEIOUS versus IOUS column indicate new findings at CEIOUS, and *regular characters* indicate same findings between IOUS and CEIOUS.
CRC = Colorectal cancer; IOUS = intraoperative ultrasonography; CEIOUS = Contrast-enhanced intraoperative ultrasonography.

Table 2. Sensitivity, specificity, positive and negative predictive values, and accuracy of preoperative imaging, intraoperative ultrasonography, and contrast-enhanced intraoperative ultrasonography in patients with colorectal cancer liver metastases

	CRC liver metastatic nodules		
	Preoperative imaging	IOUS	CEIOUS
Sensitivity	71	88	100
Specificity	0	0	0
Positive predictive value	97	100	100
Negative predictive value	0	0	0
Accuracy	70	89	100

CRC = Colorectal cancer; IOUS = intraoperative ultrasonography; CEIOUS = Contrast-enhanced intraoperative ultrasonography.

contrast-enhanced CT performed 9 months after the operation.

Resection Guidance

CEIOUS allowed better disclosure of the tumor margins of the main lesions in 7 of 24 patients (29%). The better visualization of the tumor margins enabled improved definition of the resection area, and of the liver dissection plane, resulting in easier resection guidance (Fig. 1, *A–C*).

DISCUSSION

The complete surgical clearance of the liver even for multiple CRC liver metastases or in the presence of vascular infiltration is justified because once tumor clearance is obtained, there are significant benefits in long-term survival.[9] To achieve this standard, most of the merits should be attributable to the extensive use of IOUS for staging than for resection guidance. However, tumor staging completed by IOUS did not seem fully adequate in previous reports.[3] In the present study, CEIOUS improved IOUS sensitivity in detecting new small fore sites, reducing the risk of downstaging the disease, and enhancing the rate of treatment with curative intent. Among 24 patients who underwent surgery for CRC liver metastases, 5 (21%) had new lesions discovered only by CEIOUS (Fig 1, *A*, *B*). High values of sensitivity, positive predictive values, and accuracy are biased by the facts that CEIOUS is a technique that is not an alternative to IOUS but its complement, and that CEIOUS results are confirmed by the findings at histology and follow-up, which may be lacking. However, the low rate of intrahepatic recurrence at postoperative follow-up observed in the present series (4%) seems to support the effectiveness of CEIOUS in improving the ability to detect fore sites during hepatic surgery. This ability has been confirmed by other authors who reported similar results in a comment to our published preliminary experience.[10] Furthermore, the better visualization of the margins of the main lesion (Fig. 1, *A*, *B*) in 29% of patients with CRC liver metastases enabled the surgeon to better define the resection area and proper dissection plane, ruling out the risk of tumor exposure and enhancing the treatment radicality.

The decision to operate was affected by new findings on CEIOUS in five patients (21%); to that must be added the 17% of patients who had an operative decision modified by the IOUS findings, which were confirmed by the findings at CEIOUS. Furthermore, although it is subjective, the impact of the increased visibility by CEIOUS of CRC liver metastases margins on the surgeon's surgical strategy in 29% of patients who underwent operation must also be taken into consideration.

In the last two decades the impact of IOUS on operative decision making, when compared with those of preoperative imaging techniques, has decreased from 49% to 51%[11,12] to 4% to 7%.[1,10,13] This is certainly because of the progress in preoperative imaging. However, the low rates shown in the latest reports[1,13,14] are partially motivated by the surgeon's surgical policy. In fact, because a considerable number of patients underwent major hepatectomies, new nodules detected by IOUS in the same hemiliver would not have modified the surgical strategy. In our experience, major hepatectomies are performed in the minority of patients[15] because of the extensive use of the IOUS guidance for achieving parenchymal sparing resections; thus, detection of new nodules is more suitable for changing the surgical strategy. However, CEIOUS clearly enhances the impact of IOUS on operative decision making for liver tumors either extending or reducing the resection foci. In our experience, CEIOUS allowed accurate upstaging of those five patients with CRC liver metastases who had fore sites undetected by IOUS (Table 1). Furthermore, IOUS and CEIOUS are complementary to surgery. Indeed, CEIOUS confirmed the partial downstaging obtained with IOUS in one carrier of CRC liver metastases (patient 8 in Table 1). The use of dedicated intraoperative transducers, which have been recently released, should allow an easier and more complete liver exploration and further improve the accuracy of CEIOUS. Furthermore, the expected introduction of probes fitted for laparoscopic exploration may enable CEIOUS without

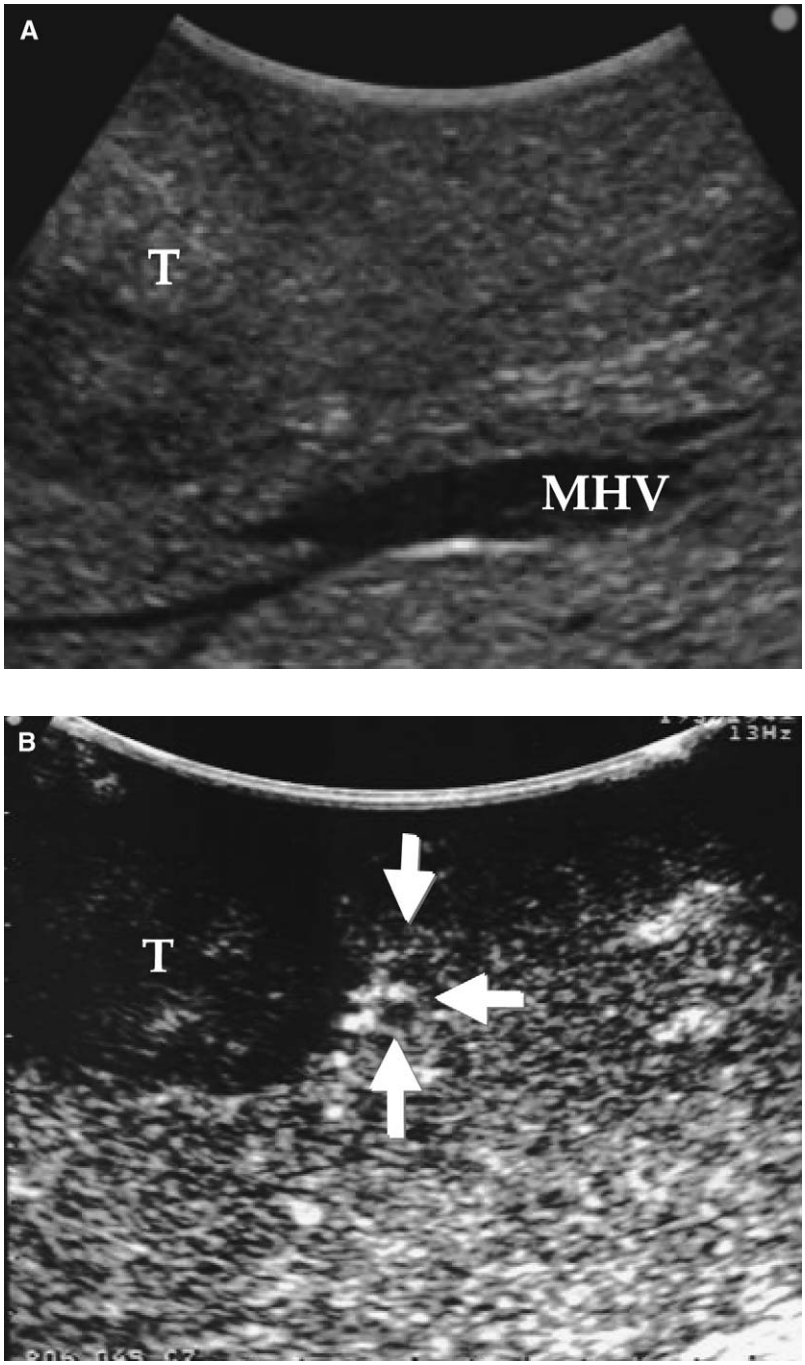

Fig. 1. (**A**) Colorectal cancer liver metastases (T) that were mainly located in segment 5 and had undefined margins at intraoperative ultrasonography (IOUS). MHV = middle hepatic vein. (**B**) At contrast-enhanced intraoperative ultrasonography (CEIOUS) the margins of the lesion (T) appear clearly visible and two tiny nodules (*vertical arrows*) are visible beside the lesion itself: These two nodules together with the edge of the main lesion were in contact with the distal part of the portal branch feeding subsegment 4 inferior (*horizontal arrow*). (**C**) This CEIOUS presentation, which was confirmed at histology, required extension of the resection to the whole subsegment 4 inferior (*arrows*).

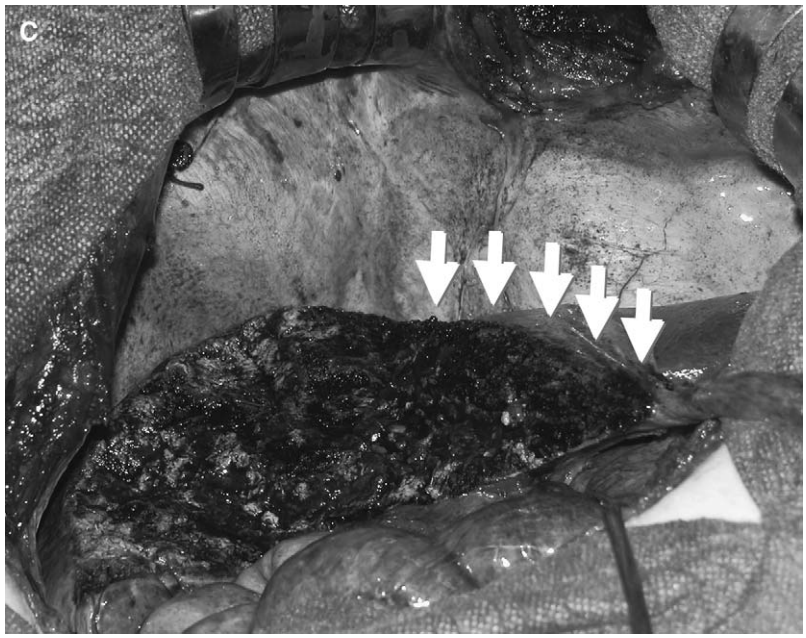

Fig. 1. *(Continued)*.

laparotomy, which may be particularly useful in a patient with hepatocellular carcinoma and who is a candidate for receiving a liver transplant.

Certainly some concerns could be raised about the adjunctive costs, required learning curve, and safety of this new technique.

As for the adjunctive costs of CEIOUS, SonoVue incurs a cost of 120 to 130 Euros per dose, which seems to us a reasonable addition considering the adjunctive information provided. Conversely, because our experience is the only one reported in the literature, it is difficult to provide a good estimation of the duration of the learning curve for CEIOUS; however, an adequate background in basic ultrasonography allowed us to obtain additional information in a relatively small series of patients, showing that progressing from IOUS to CEIOUS does not seem to require extensive training.

Some authors raised some concerns about the safety of CEIOUS.[16] As it was already discussed,[8] the European Medicine Agency temporarily withdrew approval of SonoVue for its use in echocardiography because there were three fatal outcomes reported in temporal association with the agent, which occurred in patients who had undergone cardiac imaging. In all of these patients, there was a high underlying risk for major cardiac complications, which could have led to spontaneous fatal outcome, and they did not have symptoms of hypersensitivity.

Currently, the temporary withdrawal of SonoVue approval has been suspended with the recommendation to use caution in patients with severe cardiac diseases. Patients who undergo liver resections are strictly selected patients who undergo anesthetic, respiratory, and cardiac routine evaluation to rule out major cardiovascular and respiratory diseases. Furthermore, CEIOUS is accomplished in patients who are under real-time monitoring by the anesthesiologist, who does not have to add any particular care to that usually performed for patients who undergo hepatectomy. Therefore, because patients who undergo CEIOUS are not in the category at risk for the use of SonoVue and they are well monitored during the procedure, it can be affirmed that CEIOUS is a safe procedure.

CONCLUSION

IOUS accuracy can be enhanced by the intraoperative use of second-generation contrast agents for ultrasonography. In patients with CRC liver metastases, CEIOUS allows the surgeon to better detect small fore sites, resulting in more radical hepatectomies, and is a further aid for resection guidance. These findings offer new scenarios in the staging and surgical treatment of liver metastases.

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Discussion

Dr. Henry Pitt (Indianapolis, IN): I thank Dr. Montorsi and his coauthors for sending me the article in advance, and for presenting another nice article that shows that intraoperative ultrasound is better than anything we have preoperatively to evaluate these patients, and for their attempt to prospectively validate this new technology, the contrast-enhanced intraoperative ultrasound.

My understanding is that the intraoperative ultrasound was actually too sensitive and not specific enough in detecting *nonmalignant small lesions* in patients with hepatocellular carcinoma and that routine intraoperative ultrasound is not as sensitive as contrast-enhanced intraoperative ultrasound in detecting *colorectal metastases*.

For this analysis you need the final pathology, and you have the final pathology in all the patients with colorectal liver metastases, but you don't have the final pathology in all the patients with hepatocellular carcinoma. Obviously, these small lesions can be many things: they could be regenerative nodules, hamartomas, little hemangiomas, or cysts.

Thus, I have two questions that are related. First, what percentage of those small nodules actually was removed? Second, if you couldn't see them preoperatively on MR or CT and you can't see these small lesions postoperatively on MR or CT, how do you know whether they are really growing or not? Therefore, how do you know the accuracy of this new technology?

The other issue that was unclear to me was that your authors are from Milan, Lodi, and Tokyo. So where were these studies performed?

Dr. Montorsi: Thank you, Dr. Pitt, for your comments. The problem is, above all, the assessment of HCC nodules; it is where we feel the examination would have, as you mentioned, an impact in terms of nodule differentiation rather than detection. At the beginning of our experience we resected all the new nodules we detected by IOUS despite the CEIOUS findings: all of those 10 nodules removed in which CEIOUS did not disclose any pathologic enhancement were nonmalignant. In details, at histology they proved to be high-grade dysplastic nodules (four), regenerative nodules (four), and fatty change (two). The remaining seven nodules were simply followed up with CT scan and they did not appear at the postoperative imaging (assuming them to be benign). Indeed any malignant degeneration of one of these nodules would have been shown at CT or MRI postoperatively as a growing and enhanced new nodule. Therefore, I think that the accuracy, even with the limitation of the relatively small number of patients, is approximately 100%. Histology,

for those nodules that were removed, and follow-up, for those not resected, did not show any direct or indirect sign of malignancy in B-type nodules.

One of the coauthors (G.T.) has worked for a long time in Japan as a staff member of Dr. Makuuchi, so we are in close contact with him and he gave us his supervision. However, this series was performed initially in Lodi (some coauthors are from that hospital), and then in Milan at our institution.

Dr. Thomas Howard (Indianapolis, IN): Methodologically, when you looked at your colorectal liver metastases using the contrast-enhanced and the normal intraoperative ultrasound, did you switch between using the regular ultrasound first and the contrasts-enhanced ultrasound as first or did you always use regular intraoperative ultrasound and then contrast-enhanced ultrasound as the second study?

Dr. Montorsi: In all patients we performed the conventional examination, and then in the same patients we performed the contrast examination. So every patient had two intraoperative examinations. Anyway, it must pointed out that CEIOUS is an addition to IOUS and not another diagnostic tool.

***Dr. Howard*:** Did you alter the sequence using contrast enhancement first on some occasions?

Dr. Montorsi: No, no. We first used the conventional and then the contrast.

Dr. Howard: Do you think this biases the study in any way against regular intraoperative ultrasound?

Dr. Montorsi: Carrying out CEIOUS after IOUS does not result in a bias because CEIOUS exists just as a complementary technique of IOUS. However, there were eight nodules that were not seen after conventional US but were seen only after contrast; inversely, all the nodules that were seen in the conventional US were seen even with the contrast examination.

Molecular Absorbent Recirculating System for the Treatment of Acute Liver Failure in Surgical Patients

Daniel Inderbitzin, M.D., Beat Muggli, M.D., Annette Ringger, M.D., Guido Beldi, M.D., Markus Gass, M.D., Beat Gloor, M.D., Dominik Uehlinger, M.D., Bruno Regli, M.D., Jürg Reichen, M.D., Daniel Candinas, M.D.

The Molecular Adsorbent Recirculating System (MARS) represents an attractive artificial liver support system for the treatment of liver insufficiency. However, neither indications for MARS treatment (i.e., after extended liver resection) nor criteria for discontinuation of therapy have been evaluated. Therefore, we analyzed the clinical data of all our surgical patients who received MARS treatment for acute liver failure (n = 7). The aim of the study was to identify prognostic indicators for survival. Four of 174 patients resected for hepatic malignancy at our institution received a total of 13 MARS treatments. Two additional patients were successfully bridged to orthotopic liver transplantation with seven MARS treatments and one patient was MARS supported after liver transplantation of a steatotic graft with three MARS treatments. Five of the seven patients survived and were dismissed an average of 31 days, ranging from 17 to 47 days, after the final MARS treatment. No technical complications or adverse effects were observed during the MARS treatments. Important prognostic factors for hepatic recovery and survival were indocyanin green plasma disappearance rates greater than 5%/min and an increase in clotting factor V levels after each MARS treatment. We conclude that MARS therapy can be an effective treatment of postoperative liver insufficiency in the surgical hepatobiliary unit. (J GASTROINTEST SURG 2005;9:1155–1162) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Artificial liver support, liver surgery, acute liver failure, molecular adsorbent recirculating system, MARS, indocyanin green plasma disappearance rate

Intense liver regeneration follows hepatic resections that are required for removal of primary or secondary liver tumors in humans. Excellent hepatic regeneration and an uncomplicated recovery can be expected with a 50% or greater remnant of total liver mass that corresponds to at least 1.2% of body weight (BW).[1–3] More extensive hepatectomies, such as resections of 50–70% of total liver mass, that leave smaller liver remnants can result in impaired regeneration. The minimum liver remnant needed for survival in patients is currently considered to be 0.8% of BW.[1,4–6]

Synthetic activity and detoxification capacity of the regenerating liver may fail, typically on the third to fourth day after surgery, when extended hepatic resections result in critically low remnant liver mass.[6] In these clinical circumstances the Molecular Adsorbent Recirculating System (MARS; Gambro Rostock AG, Rostock, Germany) represents an attractive artificial liver support system for the treatment of the acute liver insufficiency.[7–10] MARS uses a hollow-fiber dialysis module containing an albumin-impregnated polysulfone membrane that separates the patient's blood and the 20% albumin dialysate in the extracapillary compartment. The albumin dialysate is cleansed from water-soluble toxins by passage through a hemodialysis module, and albumin-bound toxins are removed by perfusion over activated charcoal and resin.[11]

Reports on the use of MARS for the treatment of hepatic failure after major liver resection are scarce and only 12 patients from five different groups have

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so far been described.[9,12–15] The reported patient mortality rate was 75% (9/12). Similarly, reports on the outcome of MARS therapy in the liver transplant setting, such as bridging to orthotopic liver transplantation (OLT), treatment of primary nonfunction after OLT, or therapy of delayed graft function after OLT, are limited to single reports.[9,11,16–21]

Neither clear indications for the postoperative initiation of MARS treatment, such as after major hepatic resections, nor criteria for discontinuation of therapy have been evaluated. Therefore, we prospectively analyzed clinical data from all of our surgical patients who received MARS treatment. The aim of the study was to identify prognostic parameters for survival during MARS therapy.

MATERIAL AND METHODS

The clinical data obtained from the surgical patients (n = 7) who were included in the study are summarized in Table 1. Informed consent for MARS treatment was obtained from the patients or an immediate family member (institutional approval: 1.05.01.30.-17). Indications for the initiation of

Table 1. Patient Characteristics, Diagnosis, Surgical Treatment, and Outcome After MARS Treatment

Patient (Gender, Age [yr])	Group	Diagnosis	Surgical Intervention (Resected Couinaud Liver Segments)	Indication for Initiation of MARS Treatment	MARS Cycles (n)	MARS-Responder? Comment on Clinical Course
1 (F, 30)	**Group A**	Cholangiocarcinoma	Extended left hepatectomy (I, II, III, IV, V, VIII) Hepatic vein reconstruction	Factor V <30%	3	Yes; discharged 17 days after MARS
2 (M, 65)	**Group A**	Cholangiocarcinoma	Extended left hepatectomy (II, III, IV, part. V, part. VIII) Hepatic artery reconstruction	Factor V <30%	3	Yes; discharged 31 days after MARS
3 (M, 48)	**Group B**	Gallbladder carcinoma	Extended left hepatectomy (I, II, III, IV, V, part. VIII)	Asterixis	2	No; died 1 day after discontinuation of MARS
4 (M, 64)	**Group B**	Hepatocellular carcinoma in cirrhosis (hemochromatosis)	Extended right hepatectomy (part. IV, V, VI, VII, VIII)	Asterixis	5	No; died 2 days after discontinuation of MARS
5 (F, 66)	**Group B**	Late-onset hepatic failure in autoimmune hepatitis	OLT	Asterixis	6	No; bridge to OLT. discharged 45 days after OLT
6 (M, 34)	**Group B**	Primary non-function after OLT	Re-OLT	Factor V<30%	1	No; bridge to re-OLT. discharged 17 days after re-OLT
7 (F, 65)	**Group A**	Delayed graft function after OLT (steatotic graft)	OLT	Asterixis	3	Yes; discharged 47 days after MARS

OLT = orthotopic liver transplantation; Part. = partially resected liver segment.
Group A includes all MARS responding and surviving patients. Group B contains all MARS nonresponding patients (nonsurvivors and patients successfully bridged to orthotopic liver transplantation).

MARS therapy were liver insufficiency with hepatic encephalopathy and asterixis in four of the patients and clotting factor V levels below 30% in three intubated patients.

MARS Therapy

A central venous access was established by introducing a Mahurkar dual-lumen catheter (Tyco Healthcare Switzerland Ltd., Wollerau, Switzerland). Patients were then connected to the primed MARS monitor (Gambro Rostock AG) that was operated in conjunction with a Fresenius 4000S (Bad Homburg, Germany) dialysis machine. A standard dialysate containing dextrose was used at a rate of 500 ml/min with sodium concentrations slightly above 140 mmol/L and a bicarbonate concentration of 35 mmol/L. Patient blood and albumin flow rates within the MARS monitor were adjusted between 150 and 250 ml/min. Heparin was administered to maintain activated clotting time (ACT) between 100 and 180 seconds. MARS treatment was limited to a maximum of 8 hours, followed by a 16-hour MARS-free interval.

Laboratory Parameters

Liver function tests including coagulation parameters, complete blood cell count, serum electrolytes, ammonia, and creatinine were determined before and after each MARS treatment. Indocyanin green (ICG) plasma disappearance rates (ICG-PDR) were measured after injection of 0.5 mg ICG/kg body weight (ICG-Pulsion; Pulsion Medical Systems, Munich, Germany) by the use of the noninvasive LIMON monitor (Pulsion Medical Systems).

Patient Groups

Two patient groups, based on the hepatic response under MARS therapy, were compared to identify potential prognostic factors during MARS therapy (Table 1). The two groups were MARS responders (group A, surviving patients after extended liver resections and with delayed function of a steatotic liver graft; n = 3; 9 MARS cycles) and MARS nonresponders (group B, nonsurvivors and patients bridged to OLT; n = 4; 14 MARS cycles).

Statistical Analysis

Results are expressed as mean ± SD. Data were statistically analyzed using the Jandel Scientific Software (1.0; Jandel Scientific, San Raffael, CA). *t*-Tests were used to compare normally distributed data between groups, and paired *t*-test analysis was performed to compare laboratory parameters before and after MARS treatment. For nonnormally distributed data, a Mann-Whitney rank sum test was applied to compare groups and the Wilcoxon signed rank test was used for paired analysis. The significance level was set at $P < 0.05$.

RESULTS

During the study period, 212 hepatic resections were performed in 174 patients at our institution. Only 4 patients of the 20 with extended liver resections required MARS support. Three (5.4%) of a total of 56 OLT patients received pretransplant or posttransplant MARS therapy.

Two patients from group A (n = 3), after undergoing extended hepatic resection, were treated daily for 3 days beginning on postoperative day 2. One patient with a delayed graft function after OLT received three MARS cycles 3 days post-OLT on. These three patients were discharged from the hospital 17, 31, and 47 days after MARS.

One patient from group B (n = 4), after a right portal branch occlusion and a consecutive extended right hepatectomy due to hepatocellular carcinoma (HCC) in a cirrhotic liver (hemochromatosis), was treated from day 7 to day 11. MARS was then discontinued because of a lack of clinical improvement. The patient died 2 days later. An extended left hepatectomy and right portal vein reconstruction were performed in one patient with gallbladder carcinoma. MARS treatment was initiated on postoperative day 2 and discontinued after two cycles to comply with the patient's request upon receiving histopathologic confirmation of a hepatic tumor remnant. The patient died 1 day later. Two patients in this group were successfully bridged to OLT and re-OLT and discharged 17 and 45 days after MARS treatment.

Ten of 23 MARS therapies lasted the full 8 hours. The other 13 MARS treatments were discontinued early (6.3 ± 1.5 hours) due to a filter obstruction. No differences in therapy time were observed between groups A and B. An average blood flow of 188 ± 19 ml/min and corresponding albumin flow in the MARS monitor of 237 ± 19 ml/min were used in both groups (P = NS between groups). No adverse effects were encountered during the 166 hours of MARS therapy.

The average heparin dose administered during MARS cycles was 530 ± 375 IE/hr in group A and, significantly lower, 120 ± 160 IE/hr ($P < 0.05$), in group B. A trend toward higher heparin doses with every additional MARS cycle was detected in group A. Most important, except for two minor bleeding incidents at the catheter insertion site, no severe bleeding complications were observed.

Model for End-Stage Liver Disease (MELD) Score

Initial MELD scores[22] added up to 19, 19, and 31 in group A and 15, 22, 40, and 40 in group B. MELD scores significantly ($P < 0.001$) decreased (-3.9 ± 2.2) in group A after MARS treatment; they were unchanged (P = NS) in group B (-0.9 ± 2.8).

Laboratory Parameters

Hemoglobin values and leukocyte counts did not differ between the groups, nor did MARS therapy alter these values. Initial platelet counts were similar in both groups (Table 2). A paired analysis revealed significant platelet loss during MARS treatment in group B ($P < 0.05$). Water-soluble creatinine and ammonia were efficiently ($P < 0.05$) removed by MARS therapy. Bilirubin and alkaline phosphatase levels were significantly higher ($P < 0.05$) in group B patients. Bilirubin levels only decreased in group B ($P < 0.05$) during the MARS therapy.

Coagulation Parameters

One patient in group A and two patients in group B received fresh frozen plasma (FFP) before MARS therapy. Clotting parameters obtained within 24 hours after FFP administration were excluded from analysis.

International normalized ratio (INR) values were significantly lower ($P < 0.05$) in group A both before and after MARS treatment (Table 2). In a paired analysis, INR values increased during MARS therapy ($P < 0.05$) in group B while they were unaltered in group A (P = NS). All group A patients had INR values below 2.0 at all time points. It should be noted that only patients of group B received FFP during MARS therapy.

Initial clotting factor V levels were $24.7 \pm 7.5\%$ in group A and $21.8 \pm 21.5\%$ in group B. Factor V levels increased significantly ($P < 0.05$) between MARS cycles in group A by $12.2 \pm 8.0\%$ and the average factor V levels decreased by $0.4 \pm 6.1\%$ in group B (P = NS) (Fig. 1). All patients who had clotting factor V levels spontaneously reach greater than 40% during MARS therapy recovered.

Noninvasive Measurement of ICG-PDR

ICG-PDRs were obtained before and after MARS treatment. Values remained stable throughout MARS cycles (P = NS). Average ICG-PDRs for group A patients were $7.0 \pm 1.1\%$/min. Corresponding values for group B were significantly lower ($2.5 \pm 1.1\%$/min, $P < 0.0001$) (Fig. 2). No patient with an ICG-PDR below 5.0%/min survived without OLT.

Table 2. Laboratory Parameters of Surgical Patients With Liver Failure Before and After MARS Therapy

Laboratory Parameters		Group A (n = 3) (9 MARS Cycles)	Group B (n = 4) (14 MARS Cycles)
Thrombocytes (10^9/L)	Pre-MARS	101.4 ± 51.0	87.5 ± 61.4
	Post-MARS	95.6 ± 43.2	64.2 ± 47.6*
Creatinine (μmol/L)	Pre-MARS	143.3 ± 57.7	181.8 ± 139.5
	Post-MARS	100.3 ± 30.5*	141.5 ± 115.0*
Ammonia (μmol/L)	Pre-MARS	37.9 ± 31.4	45.2 ± 37.7
	Post-MARS	26.2 ± 18.6*	35.9 ± 28.9*
Aspartate aminotransferase (U/L)	Pre-MARS	2151 ± 2178	1408 ± 1633
	Post-MARS	1254 ± 1077	1007 ± 1024
Alanine aminotransferase (U/L)	Pre-MARS	2534 ± 2713	1080 ± 1083
	Post-MARS	1804 ± 1859	932 ± 1020
Alkaline phosphatase (U/L)	Pre-MARS	75 ± 31	258 ± 113†
	Post-MARS	76 ± 29	227 ± 95†
Bilirubin (μmol/L)	Pre-MARS	115.1 ± 76.0	264.8 ± 176.7†
	Post-MARS	96.4 ± 60.3	216.4 ± 119.0*†
Prothrombin time (INR)	Pre-MARS	1.44 ± 0.26	2.22 ± 0.45†
	Post-MARS	1.41 ± 0.26	2.66 ± 0.78*†

Average serum laboratory parameters (mean ± SD) of MARS responding patients (group A) and MARS nonresponding patients (group B) before (Pre-) and after (Post-) MARS therapy are presented. A significant decrease (*$P < .05$) of thrombocyte counts was seen in group B after MARS therapy. This indicated platelet loss during treatment. Creatinine and ammonia levels in the blood decreased after MARS in both groups as expected. Significant differences (†$P < .05$) between groups A and B were detected in alkaline phosphatase, bilirubin, and INR values. In a paired anlaysis comparing values before and after MARS treatment, a significant decrease in bilirubin values (*$P < .05$) and a rise of INR (*$P < .05$) values was seen in group B only.

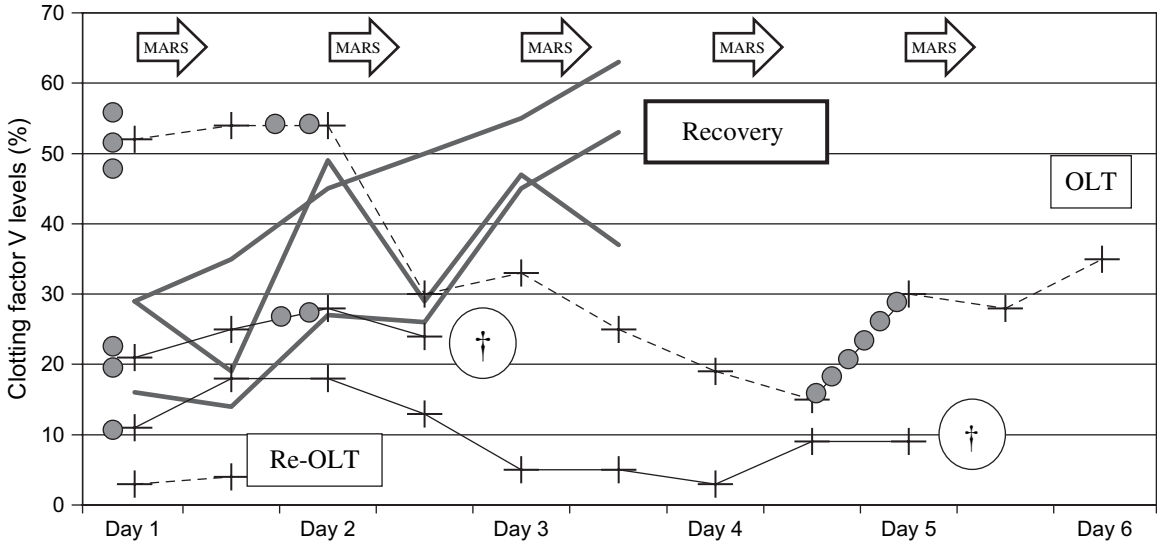

Fig. 1. Clotting factor V levels in patients with liver failure during MARS therapy. Depicted are clotting factor V levels of all patients during the entire period of MARS therapy (MARS, *arrow*). Three patients received fresh frozen plasma (FFP) (●) before the initiation of MARS therapy. Only group B patients received FFP during MARS treatment. After superurgent listing for OLT, one patient received six FFP treatments on day 5. Initial factor V levels were <30% in six of seven patients. Surviving patients (*bold line*; Recovery) showed an increase of factor V levels with each additional MARS cycle (a MARS cycle includes 8 hours of MARS treatment followed by 16 hours MARS free). Two patients died (*fine line*; †) after discontinuation of MARS treatment. Two patients (*dotted line*) were successfully bridged to OLT and re-OLT.

DISCUSSION

MARS therapy has proved to be safe for the treatment of liver failure in over 3000 patients.[9] However, the reported mortality for MARS-treated surgical patients with hepatic failure after major liver resection has been reported at 75%.[9,13–15] Patient selection for liver surgery and the indications for MARS treatment clearly influence the survival data. Complete tumor resection resulted in a small-for-size liver remnant (<0.8% BW) in three of four resected patients in this series. The remaining resected patient had hemochromatosis-related liver cirrhosis in the left liver remnant. To date, no appropriate indicators have been validated to a priori determine survival of patients with severe posthepatectomy liver dysfunction. We therefore initiated MARS therapy in surgical patients early on, when it was apparent that liver insufficiency was imminent. MARS treatment was initiated as soon as asterixis was present or, in the case of prolonged mechanical ventilation and complete muscle relaxation, when clotting factor V levels were below 30%. Similarly, we suggest the early use of MARS[9,11,16,17] as a bridge to OLT, for the treatment of primary nonfunction after OLT, and as a temporary support strategy after transplantation of a steatotic liver graft.

Several prognostic parameters correlated well with survival in this analysis. ICG-PDR values have been used for the past 20 years to monitor hepatic function after injury,[23] to assess liver function before and during major hepatic resections,[24] and to determine suitability as well as early graft dysfunction in the liver transplant setting.[25,26] In our study, ICG-PDRs remained low, less than 10%/min, despite significant clinical and synthetic improvement in the group A patients during the first days of liver supportive therapy. Noninvasive ICG-PDR monitoring seems inappropriate for the verification of successful hepatic regeneration early but was clearly able to indicate patients survival if an ICG-PDR greater than 5%/min was determined (Fig. 2). The values observed are considerably lower than those described in critically ill patients with hepatic dysfunction.[27,28] The role for ICG-PDR in evaluating surgical patients requires further prospective investigation.

Interestingly, INR and bilirubin values also correlated well with survival. They may contain a predictive value not only in the setting of chronic (MELD score)[22] but also in acute postoperative liver failure. Interestingly, the described[7] significant decrease in serum bilirubin levels during MARS therapy was observed only in group B.

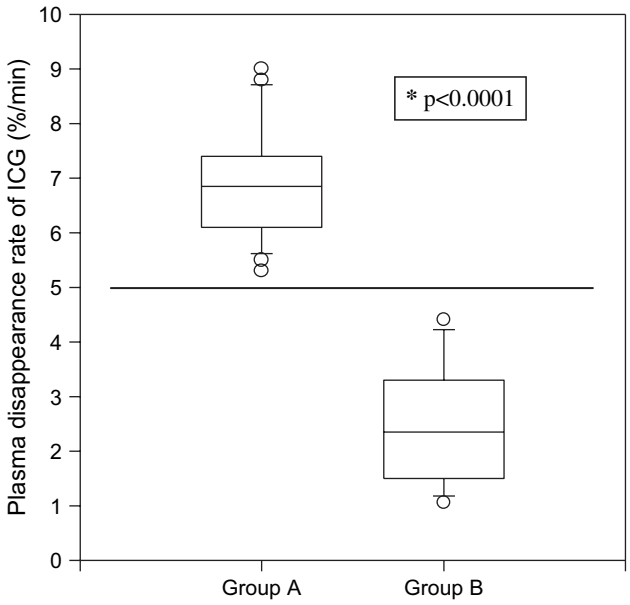

Fig. 2. Indocyanin green plasma disappearance rates (ICG-PDRs) in surgical patients with liver insufficiency. Tukey box plot: Depicted are ICG-PDR before (Pre) and after (Post) MARS treatment of MARS responding patients (group A) and MARS nonresponding patients (group B). The box boundaries indicate the 25th and 75th percentiles. The line inside the box shows the value of the 50th percentile. Capped bars indicate the 10th and 90th percentiles, and symbols mark outliers. Patients responding to MARS treatment (group A) had significantly higher ICG-PDR than nonresponders (group B). An ICG-PDR of $>5.0\%$/min appears to separate survivors from nonsurvivors ($^*P < 0.0001$).

Clotting factor V levels can predict the outcome in acute liver failure and coagulopathy.[29] For this reason we systematically assessed factor V levels before and after each MARS treatment. Factor V levels acted as a surrogate marker for synthetic hepatic activity, and we noted a significant increase between each MARS cycle in patients of group A that indicated an early improvement in liver function (Fig. 1).

The alterations in systemic heparin response and variations in heparin clearance rates in acute liver disease are well recognized.[30] Additionally, heparin elimination shows considerable interindividual variations.[31] A recent systematic review of artificial and bioartificial liver support systems from the Cochrane Hepato-Biliary group identified bleeding complications as the most important and serious adverse events during treatment of hepatic failure.[32] Therefore, we closely monitored ACT values during MARS therapy. In contrast to other reports,[10,15] no bleeding problems were observed in our series. We strongly recommend tight control of ACT values and cautious administration of heparin. Thirteen MARS Flux Dialyzers were lost during the treatment of five different patients as a consequence of this policy. Clotting of the MARS system is a nonreversible event in our experience. Neither rinsing of the system nor additional administration of a heparin bolus can rescue the filter. In cases of filter obstruction, and when elevated transmembrane pressure indicates imminent hemolysis, we reduce the blood and albumin perfusion rate and terminate the MARS treatment.

Our initial experience with MARS treatment of surgical patients with liver failure shows promising results with five of seven patients surviving. The beneficial effect of MARS therapy on our surgical patients is difficult to determine, and the potential prognostic factors identified in our series as well as the MARS system itself require further validation in additional prospective randomized controlled trials.

CONCLUSION

MARS therapy is safe and can be an effective treatment for postoperative liver insufficiency. An important prognostic factor for survival identified in our patients was an ICG-PDR of greater than 5%/min. MARS therapy represents an important therapeutic option for the treatment of severe hepatic dysfunction in the surgical hepatobiliary unit.

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Discussion

Dr. Jan Stange (Rostock, Germany): The albumin dialysis system using MARS was developed as a detoxification support system to support patients in liver failure by removing toxins from blood to improve hepatic encephalopathy and lessen the hyperdynamic circulation that leads to hypertension and kidney failure. These items are factors that alter survival. The majority of data have been collected in patients with chronic liver disease who have acute liver failure. Data of postsurgical complications that end in liver failure are rather rare, and here is what I personally think is the specific value of your presentation. In addition to postsurgical liver failure, other covariants might affect outcome. Knowing about those covariants would help us to assign the therapy to those patients who would have the biggest benefit from it.

From your presentation, the cofactors that were predictive for a good outcome can be divided into two major groups, the first group having high INR, high bilirubin, and a low indocyanine green clearance. The second group had the ability to show improvement in liver function in the phases between treatments. So in the group of patients who when off treatment have recovery of liver function, I have three questions.

First, with the exception of clotting factors or INR, your parameters, bilirubin and indocyanine

green clearance, can be signs of either poor hepatocellular function or postsurgical biliary complication. What is your personal opinion about postsurgical biliary complications in predicting outcome?

The second question — we found that a very important cofactor in dealing with liver failure is, in the presence of infection developing into sepsis, the successful treatment of the sepsis with antibiotics was important. Can you make any short comment on that?

And the third question is, usually postsurgical liver failure patients have low blood pressure and problems with hemodynamics. Usually this requires the use of continuous kidney support. For liver support, we don't know whether continuous or intermittent might be preferable. Was your specific intention to use intermittent treatments?

Dr. Inderbitzin: The answer to the first question — we treated all patients between day 2 and 3 after resection. So they were still in the phase of small liver remnant size. So these patients do have a problem with their hepatocellular mass.

Question number 2 about sepsis — we are trying to start treatment early and it is too early for septic complications. Septic complications are a contraindication in our clinic to start the MARS treatment because we are not sure about what we remove and we might even harm the septic patient with a MARS treatment. That might change in the future.

The third question was about hemodynamics. All patients were hemodynamically stable and they did not change during MARS treatment. The specific reason we chose 8 hours and intermittent treatment is that our team cannot handle the 24 hours that are also suggested by your group. That might be the future, but for the beginning, an intermittent treatment was more practical.

Dr. Steven Curley (Houston, TX): I have two questions for you. To follow up a little bit on the question that was asked previously, you presented seven patients. That is seven patients out of how many total who had an extended resection during the time you have been doing this?

Number 2, do you routinely calculate the future liver remnant on your patients to know if you are going to have a patient who may be at risk for liver insufficiency, and should those patients have portal vein embolization prior to their resection?

Dr. Inderbitzin: In the same period of time we performed 212 liver resections, including 24 extended resections that were comparable to the ones that required MARS therapy. There were four patients after resection and three patients were peri-OLT. I used the peri-OLTs as baseline of no liver function.

Unfortunately, we did not receive the liver volume from our radiologist that would allow us to determine the presence of a small liver remnant before resection. We do use the portal vein embolization. We used it in one of the described patients to induce liver regeneration.

Incidence and Management of Biliary Leakage After Hepaticojejunostomy

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This study analyzes the change in the management of biliary leakage after hepaticojejunostomy. Between 1993 and 2003 all patients (n = 1033) were studied with a hepaticojejunostomy as part of a pancreatoduodenectomy (n = 486), proximal bile duct resection (without liver resection) (n = 35), and biliodigestive bypass for malignant (n = 302) and benign (n = 210) disease. Biliary leakage was defined as the presence of bile-stained fluid (>50 mL) in the abdominal drain more than 24 hours after surgery, proven radiologically or at relaparotomy. The studied patients were divided into two equal periods to analyze the change in management. Overall, 24 of 1033 patients (2.3%) had biliary leakage. In multivariate analysis, a body mass index greater than 35 kg/m^2 ($P = .012$), endoscopic biliary drainage ($P = .044$), and an anastomosis on the segmental bile ducts ($P < .001$) were independent predictors of leakage. Management in the first half of the study period (1993–1998) versus the second half (1999–2003) was maintenance of operatively placed drains (18% vs. 15%, respectively, $P = 1.000$), percutaneous transhepatic biliary drainage (18% vs. 69%, respectively, $P = .012$), surgical drainage (55% vs. 8%, respectively, $P = .023$), and re-hepaticojejunostomy (9% vs. 8%, respectively, $P = 1.000$). There was no mortality in the patients with biliary leakage. Leakage after a hepaticojejunostomy is a relatively rare complication without mortality and can safely be managed with percutaneous transhepatic biliary drainage. (J GASTROINTEST SURG 2005;9:1163–1173) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Biliary tract surgical procedures, pancreatoduodenectomy, postoperative complications

A hepaticojejunostomy is part of the reconstruction of the biliary tract in many surgical procedures, including the pancreatoduodenectomy for periampullary neoplasms, local bile duct resection for choledochal cysts and cancer, surgical palliation of unresectable malignant biliary obstruction, drainage for chronic pancreatitis, repair after iatrogenic bile duct injury, and other procedures for other miscellaneous diseases (e.g., stone disease). Biliary leakage after a hepaticojejunostomy occurs in 0.4% to 8% of the patients depending on the type of procedure.[1–10] Leakage is often associated with a variety of concomitant complications including intra-abdominal abscess formation, pancreatic leakage after pancreatoduodenectomy, bleeding, and wound infection. Although biliary leakage occurs relatively seldom, the outcome can be disastrous, resulting in biliary peritonitis, prolonged hospital stay, and even mortality.

Biliary leakage can be managed as a first step by percutaneous drainage of the biloma under ultrasound or computed tomography guidance or with perioperatively placed subhepatic drains. Relaparotomy can be considered if dehiscence of the anastomosis is suspected shortly after the index operation to restore continuity or subhepatic drains can be placed. Because of the development of radiologic drainage techniques, percutaneous transhepatic biliary drainage (PTD) has become a more attractive and less-invasive alternative. In experienced hands, transhepatic access to the biliary system is even possible in case of nondilated bile ducts. During the past decade there has been a radical change in management of these patients from early relaparotomy,

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evacuation of the biloma, and aggressive lavage of the abdominal cavity toward percutaneous drainage of the biloma and, more recently, PTD.

In the present study, the incidence and prognostic factors for biliary leakage after a hepaticojejunostomy and the management of leakage were studied with special interest in the impact of percutaneous transhepatic biliary drainage.

PATIENTS AND METHODS

The study included all patients who underwent pancreatobiliary surgery and reconstruction with a hepaticojejunostomy (hepatic resection excluded because biliary leakage in these patients can also occur from the cut surface of the liver) between January 1993 and December 2003 at the Academic Medical Center in Amsterdam, The Netherlands. The hepaticojejunostomy was part of a pancreatoduodenectomy for benign (n = 69) and malignant (n = 417) disease, local resection of the proximal bile duct for benign (i.e., choledochal cysts) (n = 11) and malignant (i.e., Klatskin type I or II) (n = 24) disease, pancreaticojejunostomy for chronic pancreatitis (n = 51), and (prophylactic) gastrojejunostomy for unresectable periampullary and pancreatic head cancer (n = 302). Data from this cohort have been used in previous studies for other purposes.[11–15] Biliary leakage was defined as the presence of bile-stained fluid (>50 mL) in the abdominal drain more than 24 hours after surgery, proven radiologically or at relaparotomy.

The hepaticojejunostomy was generally performed using a running one-layer 3-0 Ethicon PDS II (polydioxanone) or interrupted 4-0 Vicryl sutures (Ethicon Inc., Somerville, NJ), depending on the size, quality, and level of the bile duct anastomosis. Intraluminal transanastomotic biliary drainage catheters were used occasionally (n = 70) in case of a nondilated biliary tree, and preoperatively placed percutaneous transhepatic biliary drains were left in place during surgery in patients (n = 61) who underwent reconstruction after bile duct injury.

Signs and symptoms included abdominal pain, dyspnoea, tachycardia, fever (>38.5 °C), abdominal

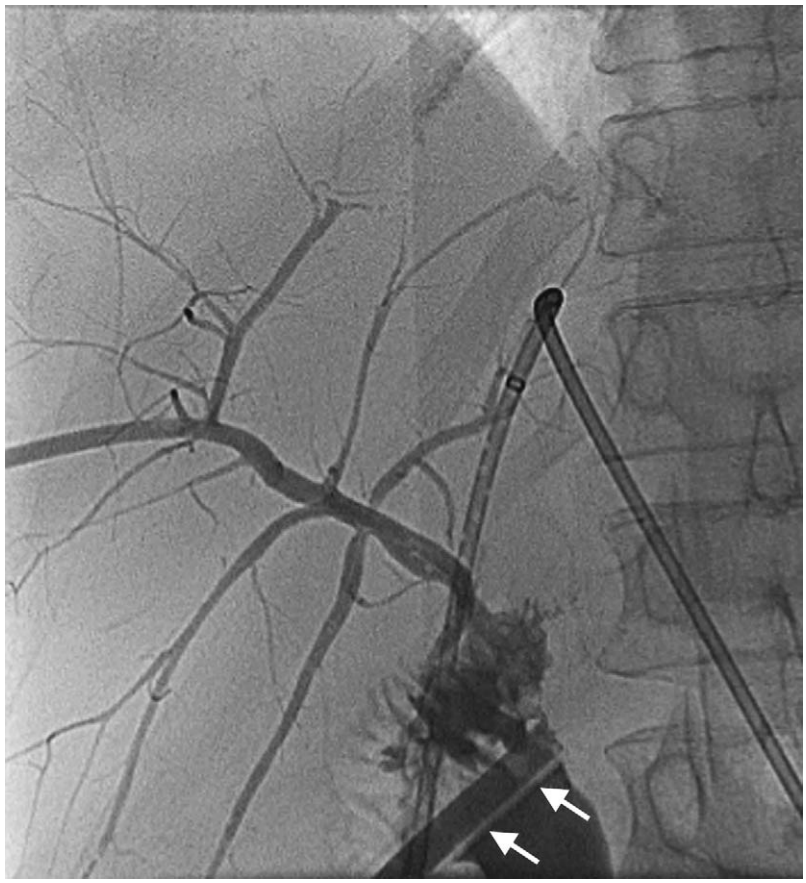

Fig. 1. Percutaneous transhepatic cholangiography after percutaneous transhepatic biliary drainage (PTD) showing leakage of the contrast medium at the hepaticojejunostomy. Contrast medium was subsequently drained into the perioperatively placed subhepatic drain (*white arrows*).

tenderness, amylase in abdominal drains (>3 times serum level), and leucocytosis ($>15 \times 10^9$/L). Diagnostic procedures were chest radiography for pleural effusion, abdominal ultrasonography, computed tomography, and cholangiography.

Leakage was initially treated by restriction of oral intake and total parenteral nutrition or true feeding and maintenance of the perioperatively placed drain depending on the procedure. Percutaneous drainage of fluid collections was generally performed if the patient developed concomitant intra-abdominal abscesses. Patients who developed biliary leakage were divided into two groups to analyze the change in management of these complications.

Surgical Management

When a relaparotomy was performed, drainage of the bilioma was carried out and the abdominal lavage was subsequently performed until the abdominal cavity was cleared of all debris. If necessary repair of the anastomosis was performed in patients with a dehiscence of the hepaticojejunostomy, subhepatic drains were placed.

Percutaneous Transhepatic Biliary Drainage

PTD for the management of this specific complication was initiated in 1997 and was carried out as follows. Access to the biliary tree was obtained through the left or right intrahepatic bile ducts.[16] With ultrasound and fluoroscopic guidance, a bile duct was punctured with a 21-gauge needle, and its position was confirmed with injection of a small volume of contrast material. A guidewire was inserted through the needle into the bile duct, and a cannula was passed over the guidewire (Fig. 1). The guidewire was advanced through the anastomosis and then exchanged for a stiffer guidewire. Over this wire a 10F polyethylene drainage catheter was placed into the bile ducts (preferably into the jejunal loop), thereby draining bile (Fig. 2). The bile was drained externally leaving the anastomosis to heal. The

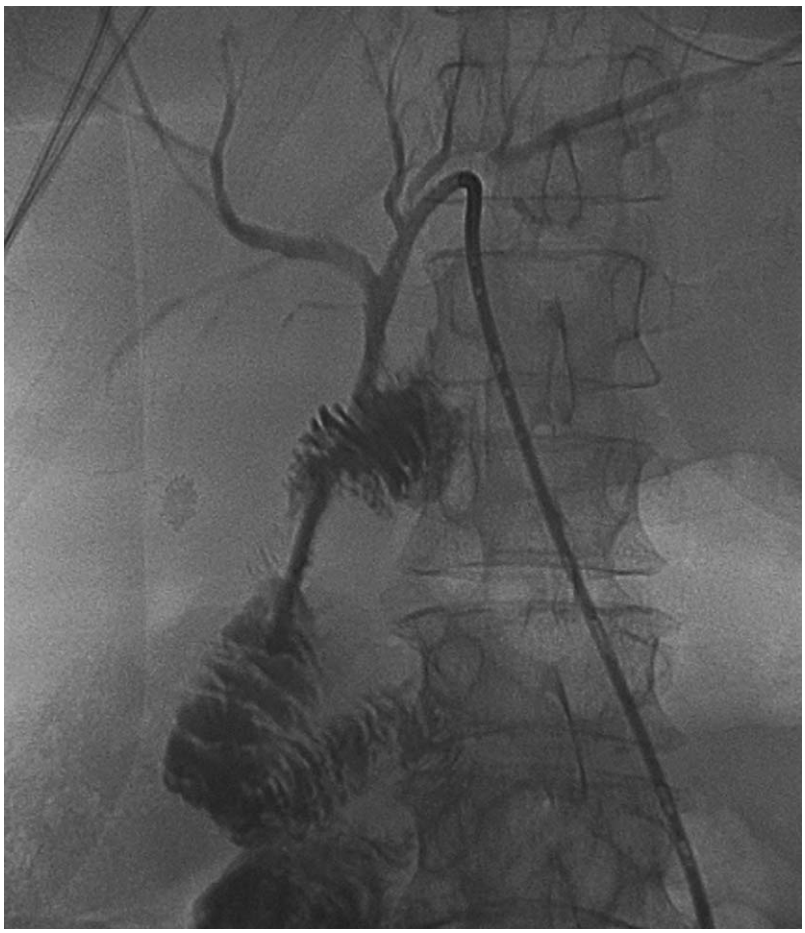

Fig. 2. A 10F catheter with drainage holes in the bile and jejunal loop is placed through the anastomosis into the jejunum through the left hepatic duct using a sub-xiphoidal approach.

external limb of the catheter was closed when signs of leakage were no longer present.

Stastical Analysis

Data analyses were performed using SPSS software version 12.01 (SPSS Inc., Chicago, IL). A P value of less than .05 was considered statistically significant. Preoperative and perioperative predictive factors were analyzed by comparing patients who had biliary leakage with patients who had no signs of this complication. A univariate analysis was first performed on the variables using Pearson chi-square test to determine which variables were significantly associated with pancreatic leakage. Fisher's exact test was computed when a table had a cell with an expected frequency of less than 5. The variables identified as significant were subsequently chosen for stepwise logistic regression to identify independent predictors for hepaticojejunostomy leakage.

RESULTS

Biliary leakage occurred in 24 of 1033 patients (2.3%) after hepaticojejunostomy. The distribution of biliary leakage is summarized in Table 1, and the incidence varied from 11% (4/35 patients) after proximal bile duct resection to 1% (3/302 patients) after a palliative bypass procedure for malignant disease. Forty-two of 486 patients (8.6%) who underwent pancreatoduodenectomy developed pancreaticojejunostomy leakage, and two patients had concomitant biliary leakage.

Table 1. Incidence of biliary leakage after hepaticojeiunostomy (1993–2003)

	Total no. of patients	No. of patients with bile leakage
Resection		
Pancreatoduodenectomy	486	11 (2.3%)
Proximal bile duct resection (without hepatectomy)	35	4 (11%)
Bypass		
Hepaticojejunostomy (bile duct injury)	119	3 (2.5%)
Hepaticojejunostomy (chronic pancreatitis)	51	1 (2%)
Hepaticojejunostomy (miscellaneous causes)	40	2 (4%)
Biliodigestive bypass in case of malignant disease	302	3 (1.0%)
Total	1033	35 (2.3%)

Predictive Factors Associated with Biliary Leakage

Univariate and multivariate results are summarized in Table 2. Univariate analysis showed that body mass index, endoscopic biliary drainage, blood loss at the index operation, and type of anastomosis were predictors for risk of postoperative leakage. Two other hypothetic factors, percutaneous biliary drainage and octreotide use, were not predictive of biliary leakage. The diameter of the bile duct was not analyzed because the data were not readily available. Multivariate analysis showed that obesity (body mass index > 35 kg/m^2), endoscopic biliary drainage, and segmental anastomosis were independent factors.

Characteristics, Symptoms, and Diagnostic Workup of Biliary Leakage

All patients but one still had a perioperatively placed drain subhepatically or through the right flank in close proximity to the pancreaticojejunostomy in place at the time of leakage (in this one patient, leakage was detected by an ultrasonography and ultrasound-guided diagnostic aspiration). The characteristics of the two groups are summarized in Table 3. The patients produced a median of 375 mL (range 50–4600 mL) of bile-stained fluid per 24 hours at the time of diagnosis. Median onset of postoperative leakage was day 4 (range 2–13 days) after the index operation. Seventeen of 24 patients (70%) presented with one or a combination of the following signs: pyrexia (54%), tachycardia (50%), increased abdominal pain (42%), peritoneal tenderness (33%), and leukocytosis (33%). Ultrasonography detected a subhepatic fluid collection in 91% (10/11 patients) of the procedures performed, and subsequent ultrasound-guided diagnostic aspiration yielded biliary fluid in 63% (5/8 patients) of the attempts.

Management of Biliary Leakage

Management of biliary leakage consisted of a conservative strategy in 18% of the patients in the first period (1993–1998) and in 15% of the patients in the second period (1999–2004) ($P = 1.000$). This consisted of antibiotics and maintenance of the perioperatively placed drains. Management and outcome are summarized in Table 4. Surgical drainage was performed significantly more often in the first period 55% (6/11 patients) compared with the second period 18% (1/13 patients) ($P = .023$). The anastomosis was judged to be sufficient in seven of nine patients

Table 2. Predictive factors associated with biliary leakage after hepaticojejunostomy (hepatectomy excluded)

			Univariate		Multivariate	
	No. of patients	Leakage	Odds ratio (95% CI*)	*P*	Odds ratio (95% CI*)	*P*
Body mass index						
<18.5 (underweight)	28	1 (4)	1.85 (0.24–14.55)	.557		
18.5–24.9 (normal weight)	766	15 (2.0)	1.00			
25–29.9 (overweight)	202	6 (3.0)	1.53 (0.59–4.00)	.383		
30–34.9 (obese level I)	28	0	0	.998		
35–39.9 (obese level II)	8	2 (25)	16.69 (3.11–89.54)	**.001**	11.32 (1.71–75.00)	**.012**
≥40 (obese level III)	1	0	0	1.000		
Endoscopic biliary drainage‡						
Yes	693	11 (1.6)	1.0			
No	340	13 (3.8)	2.47 (1.09–5.56)	**.030**	2.43 (1.03–5.78)	**.044**
Anastomosis type						
Segmental branches	44	6 (14)	8.52 (3.20–22.68)	**<.001**	13.56 (4.23–43.49)	**<.001**
Common bile duct	989	18 (1.8)	1.0			
Estimated blood loss (mL)						
≤500	203	3 (1.5)	1.0			
500–1000	175	3 (1.7)	1.16 (0.23–5.84)	.855		
1001–1500	502	8 (1.6)	1.08 (0.28–4.11)	.911		
≥1500	153	10 (6.5)	4.66 (1.26–17.24)	**.021**		
Percutaneous biliary drainage†						
Yes	117	5 (4.3)	2.11 (0.77–5.76)	.146		
No	916	19 (2.1)	1.0			
Prophylactic octreotide†						
Yes	535	13 (2.4)	1.10 (0.49–2.48)	.841		
No	498	11 (2.2)	1.0			

CI = confidence interval.

*CI denotes confidence interval. Numbers between parentheses are percentages unless indicated otherwise.

†Two variables are shown that were not significant. Other variables analyzed and not shown include age, gender, comorbidity, anastomosis (hepaticojejunostomy vs. choledochoduodenostomy), technique of anastomosis (interrupted vs. running), type and size of sutures, previous abdominal surgery, American Society of Anesthesiologists classification, smoking, alcohol consumption, preoperative laboratory workup (creatinine, hb, gGT, AF, ALAT, ASAT, bilirubin), presence of jaundice, and pylorus preservation in case of pancreatoduodenectomy. Bile duct size (only analyzed when available).

‡Endoscopic drainage by means of plastic endoprothesis (papillotomy excluded).

(78%), and drainage and debridement of the abdominal cavity were carried out. Two patients with a dehiscent anastomosis underwent a successful repair of the hepaticojejunostomy. Overall, a median of one relaparotomy (range 1–4) was performed. A relaparotomy was performed within 24 hours in five of nine patients (56%). The median hospital stay was 23 days (range 14–85 days) after relaparotomy. PTD was performed in 18% of the patients in the first period compared with 69% of the patients in the second period ($P = .012$). PTD was performed within 24 hours after onset of leakage in 6 of 11 patients (55%). Access to the biliary tree was gained through a right intrahepatic bile duct in seven patients (64%) and a left intrahepatic bile duct in four patients (36%). In two patients a relaparotomy was performed after PTD. One patient had a persistent septic state and underwent a relaparotomy 7 days after PTD; a dehiscent pancreaticojejunostomy was found during relaparotomy. The hepaticojejunostomy was intact and showed no signs of leakage. The other patient had persisted production of bile-stained fluid despite PTD, and biliary peritonitis was found at relaparotomy because of a defect in the anterior wall of the anastomosis. Overall, the failure rate of PTD was 1 in 10 patients (10%). The median hospital stay after PTD was 18 days (range 7–29 days). There were no PTD-related complications.

There was a significant decline in the relaparotomy rate (for all indications) throughout the time span of the present study, whereas the hepaticojejunostomy rate and annual number of hepaticojejunostomies performed did not change dramatically throughout the years. The annual percentage of relaparotomies, hepaticojejunostomies performed, and hepaticojejunostomy leakage is shown in Fig. 3.

Table 3. Characteristics, symptoms, and diagnostic procedures of patients (n = 24) with hepaticojejunostomy leakage

	1993–1998 (n = 11)	1999–2003 (n = 13)	*P*
Operatively placed drains still in place	10 (91)	13 (100)	.458[§]
Onset of leakage, days after surgery (median, range)	5 (2–13)	3 (1–13)	.161[†]
Signs			
Pyrexia	8 (73)	5 (39)	.093[†]
Tachycardia	9 (82)	3 (23)	**.004**[‡]
Increased abdominal pain	7 (64)	3 (23)	.095[†]
Abdomina; tenderness	5 (46)	3 (23)	.390[§]
Laboratory			
Leucocytosis $> 15 \times 10^9$/L	6 (55)	2 (15)	.082[§]
Biliary effluent in abdominal drain in milliliter (range)	400 (50–1800)	300 (100–4600)	.695[†]
Diagnostic procedures			
Ultrasonography (subhepatic fluid collection)	10 of 11* (91)	0[¶]	-
Biliary fluid found by guided aspiration	5 of 8* (63)	0[¶]	-
Computed tomography (subhepatic fluid collection)	2 of 2* (100)	0 of 1 (0)	.333[§]
Contrast extravasation during cholangiography	1 of 2* (50)	5 of 11 (46)	1.000[§]
Subhepatic abscess	2 (18)	0	.199[§]
No. of patients with a nondilated biliary duct	9 (82)	12 (92)	.576[§]

Number of successful detections/number of procedures. Numbers between parentheses are percentages unless indicated otherwise.
[†]Mann-Whitney test.
[‡]χ^2 test.
[§]Fisher's exact test.
[¶]Patients who underwent percutaneous transhepatic biliary drainage under ultrasonographic guidance were excluded.

Table 4. Initial management and long-term outcome of patients with leakage

	1993–1998 (n = 11)	1999–2003 (n = 13)	*P*
Interval between diagnosis and management	1 (0–5)	0 (1–2)	**.049**[§]
Nonsurgical			
Maintenance of operatively placed drains	2 (18)	2 (15)	1.000[‡]
Percutaneous transhepatic biliary drainage	2 (18)	9 (69)*	**.012**[†]
Surgical			
Surgical drainage	6 (55)	1 (8)	**.023**[‡]
Re-hepaticojejunostomy	1 (9)	1 (8)	1.000[‡]
Mortality	0	0	
Hospital stay after leakage in days	29 (15–69)	24 (14–139)	.283[§]
Duration of PTD drainage in days	70 (50–89)	31 (13–86)	.154[§]
Stenosis of hepaticojejunostomy during follow-up	1 (9)	1 (8)	1.000[§]
Incisional hernia during follow-up	2 (18)	3 (23)	1.000[§]

PTD = percutaneous biliary drainage.
*Two patients underwent a relaparotomy, one patient had a dehiscent pancreaticojejunostomy, and one patient had biliary peritonitis. Numbers between parentheses are percentages.
[†]χ^2 test.
[‡]Fisher exact test.
[§]Mann-Whitney *U* test.

DISCUSSION

The present study showed that clinically relevant biliary leakage after a hepaticojejunostomy occurs in only 2.3% of the patients. It was also shown that obesity, endoscopic biliary drainage, and anastomosis on the segmental ducts are independent predictors for bile leakage. Early aggressive PTD is a safe and adequate treatment strategy, and relaparotomy is seldom necessary when PTD is performed.

Because there are no clear definitions of biliary leakage after hepaticojejunostomy reported in the literature, the present study defined biliary leakage after collecting the data of all patients who had any reported bile-stained fluid in their drains after hepaticojejunostomies. Patients who had biliary leakage within 24 hours were excluded because these never progressed and resolved spontaneously, as was the case in patients who had an output of less than 50 mL of biliary effluent. These patients were deemed as having subclinical biliary leakage.

The incidence of leakage after a hepaticojejunostomy did not decrease throughout the years, whereas the relaparotomy rate decreased significantly. Proximal bile duct resections had the highest incidence of leakage. This procedure is, however, considerably different from other procedures. Obviously, most local resections include the segmental branches, and as it was shown in the present study, an anastomosis on these branches is more prone to leakage. The leakage rate after a biliodigestive bypass procedure for palliation or treatment of obstructive jaundice was low,

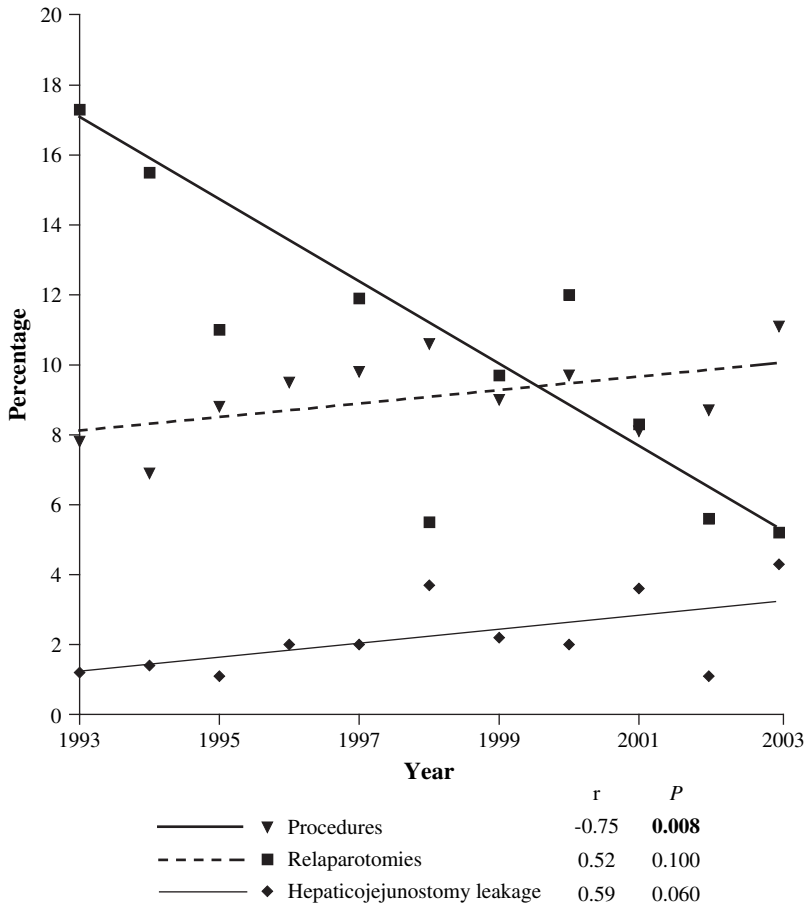

Fig. 3. The annual percentage of relaparotomies, hepaticojejunostomies performed, and hepaticojejunostomy leakage of the present study (n = 1033) from 1993 to 2003. Pearson correlation coefficient and corresponding *P* values are summarized.

adding weight to arguments that surgical palliation is adequate palliation if unresectable disease is found during surgery.[8,10,17]

The independent risk factors associated with leakage in the present study were obesity, endoscopic biliary drainage, and hepaticojejunostomy on the segmental bile ducts. It is generally more difficult to operate on obese patients, as reflected by the longer operative time.[18] Many studies failed to show a correlation between obesity and postoperative morbidity,[18–21] but these studies focused on general surgical procedures. Endoscopic biliary drainage was associated with a lower risk of biliary leakage. One possible mechanism is that the endoprosthesis induces secondary inflammation of the bile ducts, which in turn results in considerable fibrosis and thus a more patent anastomosis.[22] Another risk factor for leakage of the hepaticojejunostomy is anastomoses on the segmental bile ducts, which is obviously more technically demanding compared with anastomoses on the common hepatic duct. In the present data set, however, it was not always necessary to resect beyond the common hepatic duct. Thus, segmental anastomosis should be avoided whenever possible. The use of preoperative biliary decompression was not protective against leakage from the hepaticojejunostomy in the present study, and similar results have been reported by many studies.[23–28]

Controversy exists whether prophylactic subhepatic drains are necessary. Most surgeons around the world still use prophylactic drains to prevent leakage from the hepaticojejunostomy. However, the available evidence fails to show any benefit from prophylactic drains.[29] Because the incidence of leakage is approximately 3%, prophylactic drains are redundant in the majority of patients. An argument for placing prophylactic drains is the ability to detect leakage in an early stage. On the other hand, prophylactic drains increase the risk of ascending infection associated with these drains. Studies have shown that patients who undergo a pancreatoduodenectomy with a small duct and a soft pancreas (e.g., periampullary and

neuroendocrine neoplasms) have more complications, and that these patients would probably benefit from preoperatively placed drains.[30,31]

PTD through the anastomosis offers the chance for internal/external biliary drainage, leaving the anastomosis to heal and preventing further accumulation of bile and the development of abscesses. The complication rate (0.5%–2.5%) after transhepatic biliary drainage varies with patient status, local expertise, and diagnosis.[32–40] Patients with coagulopathies, cholangitis, biliary stones, malignant obstruction, or proximal obstruction have higher complication rates.[32,40–43] Complications related to internal/external tubes because of inadequate bile flow and tube dislodgment (sepsis and hemorrhage) can be minimized by placing a self-retaining "pig tail" tube of at least 10F through the anastomosis.[35,37,44] All patients should be treated with prophylactic antibiotics before initiating the procedures to minimize septic complications.[45,46] When a PTD is performed, the left hepatic duct is preferred because the sub-xiphoidal route used to access the left hepatic duct is less painful than the intercostal route used to approach the right hepatic duct, and because a puncture to the left duct is less likely to transgress the pleural space.[47] The complication rates are highly dependent on patient selection and are based on series comprising several hundred patients, which is a volume larger than most individual practitioners are likely to treat.[48]

CONCLUSION

Recent studies have shown the value of interventional radiology in the management of postoperative complications.[13,49] The present study adds that the management of biliary leakage after a hepaticojejunostomy has changed from an aggressive surgical strategy to an aggressive and less-invasive strategy in which interventional radiologists play a crucial role.

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Discussion

Dr. Keith Lillemoe (Indianapolis, IN): This is a very nice study, and I thank the authors for providing me the article well in advance. I think you have clearly demonstrated that the interventional radiologists are our allies in dealing with these problems and that we can avoid reoperation for complications in most of these patients. This certainly confirms our bias that the place where a patient with a bile leak needs to be is in the Infrared Radiation suite rather than back to the operating room.

The first question relates to your multivariate analysis. You provided, both in your presentation and in the text, only the factors you considered significant as predictors. I think there are some other significant factors that even if negative should be reported, such as the size of the duct. Did a nondilated duct have a greater chance of leakage than a dilated duct? Because of the controversy about the role of preoperatively placed stents, do you have any data on whether the placement of a stent before surgery

affected the leak rate?, Was there a difference between percutaneous stents versus endoscopic stents? If a patient had a percutaneous stent, such as your patients with bile duct injury, did that influence outcome?

There has obviously been debate about the use of operatively placed closed suction drains. The Memorial group has shown in a prospective randomized study on patients undergoing pancreaticoduodenectomy that drains actually increase the complication rate. Yesterday, in the M.D. Anderson presentation, they stated that they are no longer using routine perioperative drains. With this low incidence of leakage rate, would you suggest that perioperative drains not be placed in patients who have an otherwise uncomplicated biliary reconstruction?

A question about your management: Your length of stay was 24 to 29 days, and you state in your methods that most of the patients were made NPO and started on TPN. Do you really think that this is necessary in someone who has a leak with a defunctionalized limb draining the biliary anastomosis? Now, the Whipple operations wouldn't necessarily fall into that category, but how about a Roux-en-Y hepaticojejunostomy? Can't those patients eat and probably be discharged earlier? Do you use octreotide in those patients in whom there has been a leak?

Finally, I know you excluded patients undergoing hepatic resections. You did include about 35 Klatskin tumors, but as that management has gone almost exclusively to include hepatic resection, I think it would be valuable to include those patients in the analysis, because clearly, those are going to be tougher anastomoses.

It is a nice article, and I appreciate you asking me to comment.

Dr. De Castro: Thank you, Professor Lillemoe, for your kind words. Regarding your first question, the multivariate analysis, we looked at a multitude of factors and also at the size of the duct. Unfortunately the size was not always registered accurately. We did not find any correlation with the chance of leakage and the size of the bile duct in the data that were available. Patients who underwent preoperative biliary drainage either percutaneously or endoscopically before their surgery also did not have a lower or higher chance of postoperative biliary leakage.

Concerning drains placed intraoperatively, our center generally places a 27F silicone gravity drain after surgery either subhepatically or via the right flank approximating the pancreaticojejunostomy. So in the present study we were unable to analyze this variable because nearly all patients did have a drain. The reason we didn't mention these negative variables was because of the time, but these data will be included in the article; a recent meta-analysis from Pertowsky and colleagues in the *Annals of Surgery* showed that there is no evidence for routine prophylactic drainage in gastrointestinal surgery. However, the main disadvantage of not using prophylactic drains is the loss of the capability to detect biliary leakage or postoperative hemorrhage in an early phase. The article from the Memorial group mainly included patients with pancreatic cancer, and as we all know most complications occur in patients with periampullary cancer and a soft pancreas. But indeed we fully agree that for reconstruction after pancreatic carcinoma with a dilated duct and fibrotic pancreas, drainage is not useful. Patients are NPO and get TPN in case of concomitant paralytic ileus. Otherwise we encourage normal food intake. This has to be clarified in the article. Our length of stay is relatively long because of the sequelae of leakage because patients undergo either relaparotomy or percutaneous transhepatic biliary drainage. The latter are often discharged with their drains still in place and managed at our outpatient clinic.

Concerning the use of octreotide in these patients, we generally use octreotide prophylactically in patients who undergo pancreatic resection and continue this in case of leakage. Nowadays, evidence is mounting that octreotide should only be used in selected patients with a pancreatic duct less than 3 mm, and that is currently also our policy. So, some of these patients were on octreotide during the diagnosis of biliary leakage, and in our univariate analysis, prophylactic octreotide did not prevent the occurrence of biliary leakage. We do not use octreotide for the management of biliary leakage and fistulas.

Regarding your final question, we did not include liver resection because it is hard to distinguish between leakage from the cut liver surface and the hepaticojejunostomy to the remnant.

Dr. Henry Pitt (Indianaplois, IN): This presentation was very nice, and the results were wonderful. I am intrigued by the fact that the obese patients had a higher leakage rate, even after multivariate analysis. One interpretation is that intra-abdominal fat and the omentum made it very hard to get the Roux-en-Y to the hepatic hilum without tension. However, I would suggest another concept. We have recently described an entity that we call nonalcoholic fatty gallbladder disease. These obese patients may have a lot of fat in their biliary tissues, and I would suggest that bile ducts in the obese patients have fat, and maybe they don't heal as well because of fatty infiltration. What are your thoughts on this possibility?

Dr. De Castro: It would be interesting to look into that, and maybe to look into the pathology records and the bile duct resection margins of the patients who had leakage and compare these with

24 randomly selected patients who did not have leakage. Unfortunately, these details are difficult to analyze in our cohort because most patients had preoperative stents.

Dr. Andrew Warshaw (Boston, MA): Your observation was that leakage was more likely when you were anastomosing to segmental bile ducts. Is there anything more mysterious there than the fact that you have multiple anastomoses to small, fragile ducts, therefore multiple chances for leak? Also, you mentioned that some of the anastomoses were done with interrupted versus running sutures. Have you analyzed the difference in that aspect of the technique with the relative likelihood of leakage?

Dr. De Castro: Analysis of interrupted versus running sutures might introduce a bias because interrupted is used for the more difficult proximal anastomosis. We did analyze this factor, and also other technical factors of the hepaticojejunostomy, and this did not yield any results in terms of predictive factors for biliary leakage.

Obviously, an anastomosis on the segmental branch consists of two or combined anastomoses and is more prone to leakage. However, the odds ratio is much higher than one would expect given that two anastomoses result in a twofold chance of leakage. So other factors play a role, such as the relatively small size of these segmental ducts and the technical difficulty. The reason we left this in our analysis was because in some instances it wasn't necessary to dissect all the way up into the hilum, suggesting that one should only do it when it is absolutely necessary.

Laparoscopic Versus Standard Appendectomy Outcomes and Cost Comparisons in the Private Sector

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Minimally invasive surgery has been proposed as the preferred treatment strategy for various gastrointestinal disorders due to shorter hospital stay, less pain, quicker return to normal activities, and improved cosmesis. However, these advantages may not be straightforward for laparoscopic appendectomy, and optimal management of remains controversial. One hundred forty-eight patients with clinical and radiologic diagnoses of acute appendicitis treated in two different hospitals were retrospectively reviewed. Seventy-eight patients underwent laparoscopic appendectomy in hospital A and 70 patients underwent standard appendectomy in hospital B. Patients treated by either type of surgery were compared in terms of clinical and pathologic features, operation characteristics, complications, and costs. There were no significant differences between both groups in terms of clinical features, radiologic studies, complications, and final pathology findings ($P > .05$). Hospital stay was significantly shorter and bowel movements recovered quicker in the laparoscopy group. However, overall and operating room costs were significantly higher in patients treated by laparoscopy ($P < .01$). Our series show a subtle difference in terms of hospital stay and bowel movement recovery, favoring patients treated by laparoscopy. However, these results have to be carefully examined and weighed, because overall costs and operating room costs were significantly higher in the laparoscopy group. (J GASTROINTEST SURG 2005;9:1174–1181) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Acute appendicitis, appendectomy, laparoscopy

Since the development of minimally invasive surgery, there has been great interest in its application to the operation of the digestive system. This interest was initially driven by the possibility of minimal surgical trauma in operations without laparotomy leading to significantly shorter hospital stay, less associated pain, shorter return to normal activities, and improved cosmetics. Therefore, the application of laparoscopy to operations obviating the need for a laparotomy rapidly confirmed these initial expectations and became the preferred approach for cholecystectomy and for the treatment of gastroesophageal reflux disease.[1–4] Also, the significant reduction in hospital stay and medication requirements associated with the widespread development of several laparoscopy-associated instruments, has resulted in cost-effectiveness advantage favoring the laparoscopic approach.

However, these advantages may not be observed in all operations of the gastrointestinal tract. Especially in those where only a small incision is required, early hospital discharge is common, but there is a need for highly specialized and usually expensive materials.

Several studies comparing laparoscopic and standard appendectomy have shown advantages in terms of hospital stay, cosmetic results, decreased pain, and return to usual activities.[5–9] However, only few studies have pointed to increased overall costs associated with the laparoscopic approach.[6,10–12] Several factors appear to be associated with this latter issue, such as severity of the appendicitis, use of disposable instruments, and surgeon's experience. Therefore, some studies have suggested specific situations associated with improved cost-effectiveness of the laparoscopic approach in acute appendicitis.[6,7]

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In this setting, we compared the results of patients with clinical or radiologic signs of acute appendicitis treated by laparoscopic versus standard surgery by the same surgical team in two different private hospitals, analyzing surgical outcomes and specific costs. Also, overall costs were subdivided into order to identify the most important reasons for possible discrepancies between both surgical techniques.

PATIENTS AND METHODS

Patients referred to the emergency department of two different private hospitals with clinical or radiologic diagnosis of acute appendicitis were included in the study. Patients with clinical or radiologic diagnosis of diffuse peritonitis or other causes of acute abdominal pain were excluded from the study. The same surgical team managed all patients in both hospitals. Hospital choice was dependent on the patient's preference. In hospital A (Hospital Alemão Oswaldo Cruz), patients were treated only by laparoscopic appendectomy, while in hospital B (Hospital Evaldo Foz), all patients were treated only by standard appendectomy.

Laparoscopic surgery was performed under general anesthesia, open access to the peritoneum, one disposable Hasson trochar (12 mm), two reusable metal trochars, and reusable metal graspers, scissors, and dissectors. Endoscopic staplers were used for appendix resection. Specimen retrieval was performed using a plastic bag (100 ml saline solution [Baxter]). Drains were used at the surgeon's discretion.

Standard surgery was performed through a McBurney muscle-split incision with transfixation of the appendix followed by invagination of the stump by a purse-string suture on the cecum using silk 2-0. Type of anesthesia was determined by the anesthesiologist.

All patients received at least 48 hours of antibiotic prophylaxis. Use of extended periods of antibiotic was at the discretion of the surgeon. Analgesia was performed with intravenous nonopioid analgesics. Meperidine was used for patients with uncontrolled pain with nonopioid agents. Antiemetic agents (metoclopramide, dimenidrate, or ondansentron) were used only if required for nausea or vomiting. Patients were discharged after adequate oral intake, any sign of transit recovery, and no signs of infection.

Patients were compared (hospital A versus B) in terms of severity of the appendicitis (stage determined by pathology report), age, gender, days of symptoms, presence of fever, presence of leukocyte count abnormalities, duration of surgery, total hospital stay, costs, and total doses of antibiotics, analgesics, and antiemetic agents. Each item included in the study for cost considerations had identical prices for the two hospitals. Overall, hospital costs were subdivided into medication costs, operating room (OR) costs, and hospital costs. Medication costs included all antibiotics, analgesics, and antiemetic medications. OR costs included costs from the use of the laparoscopic set, disposable trocars, staplers, sutures, and standard OR charge (time dependent). Hospital costs included hospital stay (daily standard flat charge) and nursing charges for medication infusion.

Complications were also studied and included situations requiring prolonged hospital stay and requirement for readmission or reoperation. Patients with minor complications requiring no readmission or parenteral medication were not included in this complication category.

RESULTS

A total of 148 patients with clinical or radiologic diagnosis of acute appendicitis were admitted to one or the other of the two hospitals during the study period. Seventy-eight patients were treated at hospital A (laparoscopic appendectomy), and 70 patients were treated at hospital B (Standard appendectomy).

Hospital A (Laparoscopic Appendectomy)

Of the 78 patients, 41 (52.6%) were female and 37 (47.4%) were male (F/M = 1.1). Mean age was 30.9 years (SD, ±11 years), and mean duration of symptoms was 1.5 days (±1.5 days). Nineteen patients (25.0%) had history of fever (axillary temperature $>37.8\,^{\circ}C$) since first initial symptom. White blood cell (WBC) count was measured in 69 patients, resulting in leukocytosis (>11,000 cells/ml) in 47 (68.1%), leukopenia (<5,000 cells/ml) in 2 (2.9%), and normal WBC count in 20 patients (29.0%).

Abdominal ultrasonography was performed in 68 patients (87.0%), resulting in 24 nondiagnostic examinations (35.2%) and 44 examinations (64.8%) revealing signs of acute appendicitis. Abdominal computed tomography (CT) was performed in 14 patients (17.9%) resulting in 12 diagnostic (85.7%) CT examinations for acute appendicitis and 2 nondiagnostic examinations (14.3%) (Table 1).

Mean duration of operation was 99.3 minutes (±33 minutes) from draping to final skin closure. Mean number of doses was 6.8/patient (±4.6) for nonopioid analgesics, 2.5/patient for antiemetic drugs, and 0.3/patient for opioid analgesics (Table 2).

Table 1. Patient Characteristics and Clinical Presentation

	Laparoscopic Appendectomy	Standard Appendectomy	*P* value
Total No. of patients	78	70	
Gender			
Male	37 (47.4)*	41 (58.6)*	.1
Female	41 (52.6)	29 (41.4)	
Age, Median ± SD	31 ± 11 yr	26 ± 13 yr	.03
Duration of symptoms (days)	1.5	1.8	.4
Clinical presentation (n)			
Fever	19 (25.0)	21 (30.0)	.3
Leukocytosis (⩾11,000 cells/ml)	47/69 (68.1)	52/64 (81.3)	.1
Leukopenia (⩽5,000 cells/ml)	2/69 (2.9)	0	
US suggestive of acute appendicitis	44/68 (64.8)	42/62 (67.8)	.2
CT suggestive of acute appendicitis	12/14 (85.7)	6/7 (85.7)	.7

US = ultrasound; CT = computed tomography.
*Values in parentheses are percentages.

Eight patients (10.3%) had fever during the postoperative period, five patients (6.4%) developed postoperative complications, all requiring readmission to the hospital, and two patients (2.6%) required reoperation (laparotomy) (Table 3).

Fifty-nine patients had bowel movements before hospital discharge (75%), and mean interval between surgery and bowel movement was 1.3 days (±0.6 days). Total mean hospital stay was 3.1 days (±1.7 days) (see Table 3).

Final pathology report revealed ulcer-phlegmonous appendicitis in 53 patients (86.9%), gangrenous appendicitis in 3 patients (4.9%), and normal appendix in 5 patients (8.2%). In 17 patients (21.7%), final pathology report was not available (see Table 2).

Hospital B (Standard Appendectomy)

Of the 70 patients, 29 were female (41.4%) and 41 (58.6%) were male (F/M = 0.7). Mean age was 26.3 years (±13 years), and mean duration of symptoms was 1.8 days (±2 days). Twenty-one patients (30.0%) had a history of fever (axillary temperature >37.8°C) since first initial symptom. WBC count was measured in 64 patients (91.4%), resulting in leukocytosis (>11,000 cells/ml) in 52 (81.3%) and normal WBC count in 12 patients (18.7%).

Abdominal ultrasonography was performed in 62 patients (88.6%) resulting in 20 nondiagnostic examinations (32.2%) and 42 examinations (67.8%) revealing signs of acute appendicitis. Abdominal CT was performed in seven patients (10.0%), resulting in six diagnostic (85.7%) CT examinations for acute appendicitis and one nondiagnostic examination (14.3%) (see Table 1).

Mean duration of operation was 87.6 minutes (±36 minutes) from draping to final skin closure. Mean number of doses was 5.1/patient (±4.6) for nonopioid analgesics, 8.6/patient for antiemetic drugs, and 0.3/patient for opioid analgesics (see Table 2).

Seven patients (10.0%) had fever during the postoperative period, two patients developed immediate postoperative complications (2.8%), and one patient (1.4%) required reoperation (laparotomy) (see Table 3).

Sixty-five patients had bowel movements before hospital discharge (92.8%), and mean interval between surgery and bowel movement was 1.6 days (±1.1 days). Total mean hospital stay was 4.0 days (±2.7 days) (see Table 3).

Final pathologic report revealed ulcer-phlegmonous appendicitis in 47 (85.5%) patients, gangrenous appendicitis in 3 patients (5.5%), and normal appendix in 5 patients (9.0%). In 15 patients (21.4%), pathology report was not available (see Table 2).

Table 2. Surgical Time and Pathologic Characteristics

	Laparoscopic Appendectomy (n = 78)	Standard Appendectomy (n = 70)	*P* value
Operative time, mean ± SD	99.3 ± 33 min	87.6 ± 36 min	0.04
Pathologic characteristics, n†			
Normal	5 (8.2)*	5 (9.0)*	0.9
Phlegmonous	53 (87)	47 (86)	
Gangrenous	3 (4.9)	3 (5.5)	

*Values in parentheses are percentages.
†Characteristics available for 61 and 60 patients in laparoscopy and standard group and 60 patients in standard group.

Table 3. Perioperative Complications, Use of Medication, Transit Restoration, and Readmission

	Laparoscopic Appendectomy (n = 78)	Standard Appendectomy (n = 70)	*P* values
Perioperative characteristics, (n)			
Fever	8 (10.3)*	7 (10.0)*	.5
Complications	5 (6.4)	2 (2.8)	.2
In-hospital need of pain or antiemetic medication (n)			
Nonopioid pain medication (doses/patient)	6.8	5.1	.1
Opiod pain medication (doses/patient)	0.3	0.3	.9
Antiemetic (doses/patient)	2.5	8.6	<.001
Intestinal transit restoration			
Mean interval between operating room and bowel movement	1.3 days	1.6 days	.03
Rehospitalization (n)			
Readmissions	5 (6.4)	0	.06
Reoperations	2 (2.6)	1 (1.4)	.5

*Values in parentheses are percentages.

There were no significant differences between both groups in terms of gender distribution, duration of symptoms, leukocyte count, radiologic (ultrasonography and CT findings), occurrence of postoperative fever, complications, hospital readmission and reoperation rates, and doses of analgesic medications (opioid and nonopioid) or final pathological report diagnosis ($P > .05$).

Patients of hospital B (standard appendectomy) were significantly younger than patients from hospital A ($P = .03$). Patients treated with laparoscopic appendectomy had significantly longer operation duration ($P = .043$), shorter interval between surgery and first bowel movement ($P = .032$), and shorter overall hospital stay ($P = .022$). Also, patients treated by laparoscopic appendectomy required significantly fewer doses of antiemetic medications.

Costs

In patients treated by laparoscopic appendectomy (hospital A), mean overall cost was R$ 5,925.00/patient, while mean overall cost in patients treated by standard appendectomy (hospital B) was R$ 3,566.00 ($P < .001$).

Considering categories separately, in hospital A mean medication, OR, and hospitalization costs were R$ 355.2, R$ 3.575, and R$ 1,995, respectively. In hospital B, mean medication, OR, and hospitalization costs were R$ 540.0, R$ 534.1, and R$ 2,492, respectively. Even though medication and hospitalization costs were higher in hospital B, these differences were not significant. On the other hand, OR costs were significantly higher in hospital A ($P < .001$) (Table 4).

DISCUSSION

The overall lifetime risk of undergoing an appendectomy is around 10%.[13] This operation is considered to be the most frequent procedure performed in the emergency setting worldwide.[14,15] However, optimal management is still controversial.[16–18]

Table 4. Operating Room (OR) Time, Length of Stay, and Costs

	Laparoscopic Appendectomy (n = 78)	Standard Appendectomy (n = 70)	*P* value
Mean OR time ± SD	99 ± 33 min	87 ± 36 min	0.04
Mean length of stay ± SD	3.1 ± 1.7 days	4 ± 2.7 days	0.02
Costs in R$ per patient*			
Average medication costs	355	540	0.1
Average OR costs	3,575	534	<0.001
Average hospital charges (excluding OR and medication)	1,995	2492	0.07
Overall average cost	5,925	3,566	<0.001

*1 US$ ≈ 2.50 R$.

The advantages associated with minimally invasive surgery observed for cholecystectomy have been proposed as arguments for the use of laparoscopy in acute appendicitis.[6,7] In fact, morbidity and mortality rates between laparoscopic and conventional appendectomy are comparable, allowing safe comparisons between the two procedures in terms of costs, hospital stay, and other parameters in order to determine optimal treatment strategy.[6,19]

The study of laparoscopic versus conventional appendectomy has been addressed in some randomized trials when we consider only therapeutic laparoscopic procedures excluding diagnostic laparoscopy. These trials have gathered small number of patients and have not drawn definitive conclusions. A recent systematic review of 54 studies regarding therapeutic laparoscopic versus open appendectomy showed some advantages of the laparoscopic approach such as decreased rates of wound infections, pain, and hospital stay and earlier return to normal activities.[5,8] Aside from systematic reviews, it is estimated that a considerably large number of patients in a single randomized study is required in order to demonstrate significant differences in terms of complication rates between the two types of appendectomy.[1] This reflects the subtle differences between the two procedures and indicates the necessity of enrolling multicenter studies in order to obtain definitive conclusions over the best treatment option.[1] In fact, when we look closely at the numbers reported in this same systematic review, these very subtle differences become evident. First, there was significant heterogeneity between studies regarding most of the outcomes.[5,20] There is, however, some data that appear to be homogeneous among most of the studies. There was no heterogeneity regarding infectious postoperative complications leading to increased wound infections in open appendectomy and increased intra-abdominal abscesses in laparoscopic appendectomy. However, the definition of "wound infection" may be so broad in each of these studies that we are avoiding a simple wound erythema by performing laparoscopic surgery.[9]

Other than these infectious postoperative complications, all other outcomes, including duration of surgery, postoperative pain, hospital stay, return to activities, and costs, showed significantly discrepant results between studies.[5,8,20] Besides analyzing heterogeneity, differences, although significant, may still be very subtle. For instance, in terms of pain, laparoscopy resulted in a reduction of pain of 9 mm of the visual analog pain scale. This variation, however, has been shown to be under the level of pain that an average patient is able to perceive.[5]

In our study of 148 patients, the two groups were similar in terms of disease severity; there were no significant differences of duration of symptoms, WBC count, radiologic findings, and final pathologic examination, even though patients treated by standard appendectomy were significantly younger.

Operative time was significantly shorter in patients treated by standard appendectomy (99 versus 87 minutes). Results reported by others are highly variable but show either similar operative times or shorter times favoring standard technique. In fact, it has been observed that such differences have been minimal in the more recent years, possibly related to the learning curve associated with laparoscopic appendectomy. In our study, this learning curve effect might have not contributed to these longer operative times in laparoscopic approach, because the surgeons performing operations are very experienced with laparoscopic surgery, including highly complex procedures such as splenectomy and colorectal surgery. Furthermore, a reasonably large number of patients, such as 70 performed by a single surgical team, seems to be an adequate number to overcome such learning curve effects in simple operative procedures such as appendectomy. This is also reflected by a considerably narrow range of operative time observed in our series (99 ± 32 minutes). On the other hand, these longer operative times that were frequently reported with the laparoscopic approach may have significant consequences in cost comparisons. Moreover, each minute of laparoscopic surgery requires general anesthesia maintenance, whereas the standard appraoch allows regional anesthesia in selected patients, further reducing costs and possibly morbidity associated with prolonged endotracheal intubation and mechanical ventilation.

Total hospital stay was significantly shorter in patients treated by laparoscopy. This difference also led to significant implications because a difference of almost 1 day (3.1 versus 4 days) between the two groups was sufficient to reduce hospitalization costs. It should be noted that the fact the groups were treated in different hospitals could lead to a bias related to a possible preference by the surgeon for either hospital. This bias could lead to earlier patient discharge in one of the hospitals, especially in busy urban, metropolitan areas where access from one area to another is not always straightforward. Even though it has been shown that hospital stay is decreased following laparoscopic appendectomy in most of the studies, this outcome has to be considered with caution. First, there is some heterogeneity between studies.[6,21] Also, several factors appear to influence this outcome, such as hospital factors, social habits, and diverse regional health care

policies (especially in different countries).[22–24] Interestingly, one study in a highly controlled military area that included only male patients with acute appendicitis found similar hospital stay periods between open and laparoscopic approaches. This kind of population also allowed more accurate data on return to activities due to both homogeneity of "normal" activity and appropriate documentation of such outcome. In this study, return to normal activity was slightly earlier for the open group.[25] Again, this outcome (return to "normal" activity) may depend on several factors such as health care provider instructions, kind of activity, and the patient's motivation.[26]

Bowel movements were observed significantly earlier in the group of patients managed by laparoscopic appendectomy. This subtle difference could be associated with earlier patient discharge leading to a questionable benefit of the laparoscopic approach, because there seems to be no other significant consequences for the group treated by standard appendectomy. In fact, a recent retrospective study demonstrated a significant increase in postoperative gastrointestinal complications associated with open appendectomy compared with the laparoscopic approach.[9] Interestingly, this difference was not observed for other systems such as cardiac, pulmonary, or urinary.[9] In our study, overall complication rates were similar in the two groups, even though a larger series of patients may be required to prove some significant differences in the future between laparoscopic and standard appendectomy.

Even though there have been conflicting results, it is generally accepted that costs are increased in laparoscopic appendectomy compared with open surgery.[5] A large retrospective analysis from the Pediatric Health Information System (PHIS) indicated an 18% increase in charges associated with the laparoscopic approach.[1] In a randomized trial, it has been shown that the difference in the hospital bill for patients treated by laparoscopy reached 3,000 US. Considering the large yearly volume of such operations (approximately 200,000 per year in the United States), the expected increase in total hospital bill in 1 year would be over 750 million US if all operations were performed laparoscopically.[27] Others have reported a 30% cost increase with this treatment strategy, and even after standardization of technical and material aspects, there was still a 600 US difference between strategies.[25] This difference is mainly attributed to consumable OR material and may not be counterbalanced by decreased hospital stay, analgesia requirement, and return to activity.[25,28] Interestingly, when laparoscopic appendectomy was performed for a normal appendix, not only were costs significantly higher but also infection rates, hospital stay, and ultimately mortality were worse than for laparoscopic appendectomy for acute appendicitis.[29] In fact, laparoscopy was expected to decrease the frequency of appendectomy for normal appendix.[29] However, in our study, rates of normal appendices seen at pathology were similar for the two groups.

On the other hand, a retrospective study gathering data from the University Health System Consortium Clinical Data Base, comprising 60,000 appendectomies requiring over 23 hours of admission, showed similar costs related to both treatment strategies.[30] However, in this study most patients treated by laparoscopy had less advanced disease and significant comorbidities; this may have contributed to this apparent similarity.[30]

In terms of medications, patients treated by laparoscopy required less antiemetic drugs even though they required more analgesics compared with patients treated by standard appendectomy. These differences resulted in higher but not significantly different costs associated with medication in patients treated by standard appendectomy.

Therefore, considering cost issues, even though medication and hospitalization costs were separately but not significantly different between the groups, OR-related costs were significantly higher in patients treated by the laparoscopic approach. This extremely higher cost for OR in the laparoscopy group was sufficient to determine significant differences when overall costs are compared between groups. Overall, difference in the hospital bill was R$ 2,400 (approximately 800 US) per patient, a similar difference as in some reports in the United States.[25]

In conclusion, laparoscopic versus standard approach for acute appendicitis in our series led to subtle differences in terms of hospital stay and recovery of bowel movements, favoring patients treated by laparoscopy. Together with the better cosmetic results with laparoscopy, these advantages should be carefully examined in the setting of acute appendicitis. In turn, overall and OR-related costs were significantly higher for this same group of patients. Surgeons must consider these issues when choosing between these procedures. Even though laparoscopy may offer comfortable and safe full abdominal cavity access allowing complete blind removal and organ assessment during appendectomy, these advantages may not result in patient care improvement or benefit. Therefore, laparoscopic appendectomy should be viewed with caution in the management of acute appendicitis. A clear benefit for patients in terms of complication rates and recovery has not yet been demonstrated. On the other hand, benefits for the

endosurgery industries with laparoscopic appendectomy is easily estimated, because overall costs (and hospital bills) are significantly increased almost exclusively due to OR-related costs when laparoscopy is used compared to the standard approach. Possibly, the laparoscopic approach may have some advantages for patients in selected situations, such as morbid obesity and diagnostic uncertainty for abdominal pain. However, standard appendectomy remains an option with comparable results but significantly lower costs for the treatment of acute appendicitis, an issue of great importance especially in developing countries, if not worldwide.

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Discussion

Dr. Robert Beart (Los Angeles, CA): I want to thank Dr. Perez for the opportunity to review the manuscript ahead of time and once again congratulate him and his group for their continued critical review of their work and the use of that work to challenge some of the paradigms, when

appropriate, that are evolving or have been present for a while in colorectal surgery.

Certainly the design with two surgeons in two different hospitals isn't exactly a randomized prospective trial; the numbers are fairly small, at 148; and the differences, as I think the point of the paper points out well, in length of stay are quite small. The costs are substantially different, which is interesting, and certainly these sort of results have been challenged by other studies.

The seminal point in the paper is that sometimes differences we measure that are statistically significant are not truly meaningful. They don't have clinical relevance to those of us who are taking care of patients on a regular basis, and for this I think they are to be congratulated. If I were to try to paraphrase this in the words of more distinguished people, I might quote one of our former presidents, who pointed out that the question really is what the definition of "is" is.

The experimental design ignores the advantage of laparoscopy for diagnostic clarity in, for instance, women with the question of pelvic inflammatory disease. It also ignores the fact that many older patients may have perforated disease and might be better treated with an open technique. I wondered if there were any patients who fell into those categories.

There was a larger statistical variation in length of stay in the open group. Were there significant outliers who skewed the results? Were any techniques used to reduce the costs in laparoscopic surgery? For instance, using a stapling device adds substantially to the cost of an appendectomy, and there might be other ways you could reduce the cost.

Dr. Perez: Thank you very much for those excellent questions. Is there some bias in the study? The two surgeons actually performed operations in both hospitals. So there were no differences between surgeons and hospitals. The same two surgeons performed operations in both hospitals, either the laparoscopic or the open appendectomy.

The next question deals with costs. If we still want to perform laparoscopic appendectomy in specific situations, we might want to look at cost reduction, and we can do that most easily by avoiding some of the laparoscopic consumables, such as a disposable trocar, but most importantly, by avoiding the linear stapler. Now, there have been some studies comparing linear stapling devices and loops and ties, and they appear to be equivalent in results; however, the use of loops and ties may in fact lead to increased operative time and further increased costs.

Regarding the severity of acute appendicitis such as perforated cases or either diagnostic laparoscopy, these patients were not included in our study. We definitely think that there is a place for diagnostic laparoscopy as well as specific situations where a laparoscopic approach for acute appendicitis might be preferable.

As to the question about outliers, we couldn't determine what happened to these patients that actually made them stay longer in the hospital. Again, most of the literature supports that length of stay and hospital stay are more related to tradition and geographical or regional factors than the operation itself. I think that might be the case.

Dr. Jorge Szauer (Caracas, Venezuela): I enjoyed your paper very much. In our country laparoscopic surgery is becoming a luxury because of the costs and that is a terrible thing. There used to be a time when you just did the surgery and you didn't care about the costs, but now more and more this becomes a seminal issue. As surgeons with a responsibility to the community, we have to try to make these procedures more economical so people can afford it, whoever is paying for them.

I may suggest that the laparoscopic technique be done just as an open technique; for example, if you cut the appendix and the mesoappendix with an ultrasonic shears that vaporizes the tissues, then you only have to invaginate the stump with a laparoscopic stitch. This will be much cheaper than using staples. Thank you very much.

Dr. Perez: What we have shown in our paper is that if you do a standard appendectomy, it might be better, except for highly selected cases, which Dr. Beart has mentioned might best be done with the laparoscope, such as obesity, perforated cases, or for diagnostic purposes.

Adenocarcinomas of the Jejunum and Ileum: A 25-Year Experience

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Adenocarcinomas of the jejunum and ileum are rare gastrointestinal malignancies. Because few large published experiences exist, we reviewed patients with jejunal and ileal adenocarcinoma treated at our institution over the last 25 years. Between January 1976 and December 2001, 77 patients had an operation for a jejunal or ileal adenocarcinoma. Records were retrospectively reviewed for patient, tumor, and treatment variables. Factors affecting disease recurrence and patient survival were investigated.

Fifty-two of the adenocarcinomas (67%) occurred in the jejunum and 25 occured in the ileum (33%). Mean patient age was 63 ± 14 years. Segmental bowel resection was performed in 50 patients (65%) with curative intent. Palliative operative procedures including resection or bypass were performed in 27 patients (35%). One (1%) patient had stage I, 18 (23%) stage II, 19 (25%) stage III, and 39 (51%) stage IV adenocarcinoma at diagnosis. Postoperatively, 12 patients had palliative and 18 adjuvant chemotherapy (n = 30), radiation therapy (n = 1), or combination treatment (n = 7). Median patient survival was 19 months. Sixty-six percent of patients who had a curative operation had a tumor relapse. Tumor stage had a highly significant effect ($P < 0.0001$) on median survival (72 months for stage I and II, 30 months for stage III, and 9 months for stage IV disease). In multivariate analysis of patients having curative treatment, tumor recurrence ($P < 0.0001$), stage ($P < 0.0002$), and weight loss ($P < 0.001$) were significant negative prognostic indicators.

Most patients with adenocarcinoma of the jejunum or ileum present with advanced disease. Tumor stage, disease recurrence, and weight loss predicted patient outcome following a curative operation. Early recognition of these tumors requires a high index of suspicion. (J GASTROINTEST SURG 2005;9: 1182–1188) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Small bowel adenocarcinoma, surgical treatment, survival, local recurrence

Small bowel cancers are a rare and challenging problem for diagnosis and effective treatment. Despite the fact that the small bowel has the largest mucosal surface area in the gastrointestinal (GI) tract, only 1%–2% of all GI tumors occur in the small intestine.[1–3] Adenocarcinoma (ACA) occurs most often in the duodenum, and with diminishing frequency, in the jejunum and the ileum. The lack of specific symptoms and rarity of small bowel ACA contribute to advanced-stage presentations. Because the surgical treatment of duodenal adenocarcinomas differs from jejunal and ileal cancers due to anatomic considerations, we decided to evaluate the latter group of patients separately, unlike many reported experiences with small bowel cancers.[3–7] Segmental bowel resection generally provides sufficient margins for adenocarcinomas of the jejunum and ileum. No standard adjuvant chemotherapy or radiotherapy is currently recognized. This retrospective study evaluates a 25-year experience at a tertiary referral center in an effort to identify prognostic factors for patient survival and to better define appropriate

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treatment strategies in the management of jejunoileal adenocarcinomas.

PATIENTS AND METHODS

Between January 1976 and December 2001, 77 patients diagnosed with ACA of the jejunum or ileum were treated surgically at Mayo Clinic. All medical records were reviewed retrospectively. Data regarding patient demographics, presenting symptoms, predisposing risk factors, diagnostic studies, operative procedures, tumor characteristics, and nonsurgical treatment were collected. Operative management consisted of either en bloc tumor resection, including adherent structures, with curative intent or a segmental bowel resection or bypass procedure for the palliation of advanced cancer.

Statistical Analyses

Actuarial patient survival was calculated from the date of the operation using the Kaplan-Meier method.[8] Univariate tests of association with discrete risk factors were made using the log-rank test.[9] For continuous risk factors, the Cox proportional hazards model was used.[10] The Cox proportional hazards model was also used in multiple variable models, with stepwise and forward selection procedures used to select the final models. Overall patient survival was analyzed to identify adverse prognostic variables.

RESULTS

Patient Demographics and Presentation

Of the 77 patients, 43 were men and 34 were women. Mean patient age was 63 ± 14 years. Fifty-two of the ACA (67%) occurred in the jejunum, and 25 occurred in the ileum (33%). Presenting symptoms and signs included a wide spectrum: most commonly pain, followed in prevalence by nausea and vomiting, anemia, weight loss, gastrointestinal hemorrhage, fatigue, and abdominal mass (Table 1).

Table 1. Adenocarcinoma of the jejunum and ileum, presenting signs and symptoms

Presenting signs & symptoms	%
Pain	66
Nausea and vomiting	51
Anemia	38
Weight loss	23
GI bleeding	19
Fatigue	18
Abdominal mass	9

Preoperative diagnostic studies included one or more of the following: small bowel follow-through 60%, abdominal CT scan 48%, extended upper endoscopy 30%, abdominal X-ray 16%, colonoscopy 14%, enteroclysis 8%, hypaque enema 4%, and ultrasonography 1% (Table 2). These numbers do not reflect our current practice, because many patients were evaluated early in the CT era. Small bowel follow-through had the highest yield for a specific diagnostic result of 65% (n = 30/46). The value of extended upper endoscopy was limited by the location of the tumors; a diagnosis was established in 30% (n = 7/23) of patients. Abdominal CT scan was the most useful examination for detecting metastases (34%, n = 12/35).

Predisposing risk factors for adenocarcinoma were present in 14 patients, representing 20% of all patients. The majority of these patients had Crohn's disease (Table 3). Small bowel cancer represents a well-known, but infrequent, complication of this condition.

Operative Procedures and Tumor Stage

Fifty patients (65%) underwent segmental bowel resection, including en bloc resection of adherent structures (14 patients), with curative intent. Palliative operative procedures, including a resection or bypass, were performed in 27 patients (35%). Twenty patients (26%) had an emergency operation for perforation (n = 1) or obstruction (n = 19). Twelve of these patients (60%) had potentially curative operations. Pathologic evaluation revealed most patients had advanced tumor (T) stage. T3 and T4 lesions were present in 98% of the patient population. Nodal metastases were documented in 44% of the pathologic specimens. Distant metastasis was present in 51% of patients at the time of operation. Using the current AJCC staging system (6th edition),[11] one (1%) patient had stage I,18 (23%) stage II, 19 (25%) stage III, and 39 (51%) stage IV ACA at diagnosis.

Postoperative therapy

Chemotherapy was the mainstay of postoperative treatment. Thirty-six percent of the patients who had curative resection and 44% of the patients who had palliative operations received postoperative chemotherapy. Out of 37 patients who received chemotherapy or a combination of chemotherapy and radiation therapy, fluorouracil and leucovorin were the most commonly used drugs (n = 20, 51%), followed by fluorouracil alone in 14% (n = 5) of the patients. Other chemotherapy regimens included single-drug regimens: TNF, L-alanine, 6

Table 2. Preoperative diagnostic studies

	Small bowel follow-through n (%)	CT scan n (%)	Extended upper endoscopy n (%)	Abdominal X-ray n (%)	Enteroclysis n (%)	Other n (%)
Diagnostic	30 (65)	6 (17)	7 (30)	0	1 (17)	0
Nonspecific Diagnostic	12 (26)	11 (32)	0	9 (75)	1 (17)	1[a] (6)
Diagnostic for metastasis	0	12 (34)	0	0	0	3[b] (18)
Nondiagnostic	4 (9)	6 (17)	16 (70)	3 (25)	4 (66)	13[c] (76)
Total	46	35	23	12	6	17

[a]Barium enema (n = 1).
[b]Abdominal ultrasonography (n = 1), chest X-ray (n = 2).
[c]Colonoscopy (n = 11), barium enema (n = 2), angiogram (n = 1).

thioguanine, or irinotecan (one patient each) and combination therapies: fluorouracil, leucovorin, and irinotecan; fluorouracil, leucovorin, and VP-16; and irinotecan, fluorouracil, leucovorin, irinotecan CPT-11, and oxaliplatin; fluorouracil, cyclophosphamide, streptozotocin, and Adriamycin (one patient each); and fluorouracil, adriamycin, and mitomycin (n = 2). Three patients received chemotherapy elsewhere, and the drugs used were not recorded. Radiation alone (n = 1, 1%), or in combination with chemotherapy (n = 7, 9%), was less frequently used.

Patient Outcome

Median overall patient survival was 19 months, and actuarial 5-year patient survival was 24% (Fig. 1). We compared patients who underwent an operation with curative intent versus a palliative resection. There was a clear survival benefit for a curative resection (32-months median survival) compared to palliative treatment (9-months median survival). Curatively resected patients achieved a 36% 5-year survival, whereas none of the palliative group survived more than two years (Fig. 2). Tumor stage had a highly significant effect on median patient survival. The median survival was 72 months for stage I and II patients, 30 months for stage III, and only 9 months for state IV disease ($P < 0.0001$) (Fig. 3).

Two thirds (66%) of patients who had a curative operation relapsed. T4 cancers ($P < 0.0002$), tumor recurrence ($P < 0.0001$), and weight loss ($P < 0.02$) were adverse prognostic indicators in univariate analysis of patients having curative treatment. Patient symptoms, an emergency versus elective operation, and adjuvant therapy had no significant impact on patient survival. In multivariate analysis of patients having curative treatment, a tumor recurrence ($P < 0.0001$), tumor stage ($P < 0.0002$), and weight loss ($P < 0.001$) (Fig. 4) were significant negative prognostic indicators.

Table 3. Predisposing conditions for adenocarcinoma of the jejunum and ileum

Predisposing conditions	No. of patients
Crohn's disease	9 (11)
FAP	2 (3)
Celiac disease (sprue)	1 (1)
HNPCC	1 (1)
Other GI polyposis	1 (1)
Total	14 (20)

FAP = familial adenomatous ployposis; HNPCC = hereditary nonpolyposis colon cancer; GI = gastrointestinal.

DISCUSSION

Small intestinal adenocarcinomas are rare malignancies. Few reports in the literature address only jejunal and ileal ACA. Most of the reported series combine all small intestine malignancies, including adenocarcinomas, carcinoids, lymphomas, and sarcomas. Because of the different natural history and small numbers of ACA, conclusions are hard to reach for ACA of the jejunum and ileum.[12–15] We report 77 patients with jejunal and ileal ACA, treated over 25 years at a single center. This represents one of the largest published series (Table 4). Although Dabaja et al. reviewed 82 jejunal and ileal ACA, operative treatment was offered to only 83% of patients, and complete follow-up was available for only 59 of the patients.[15]

Nonspecific symptoms and the limited accuracy of many diagnostic studies contribute to the frequent advanced-stage disease at presentation. Pain, nausea and vomiting, weight loss, and anemia occur with most GI malignancies and many benign gastrointestinal conditions. The evaluation of the longest segment of the intestinal tract is imperfect because it

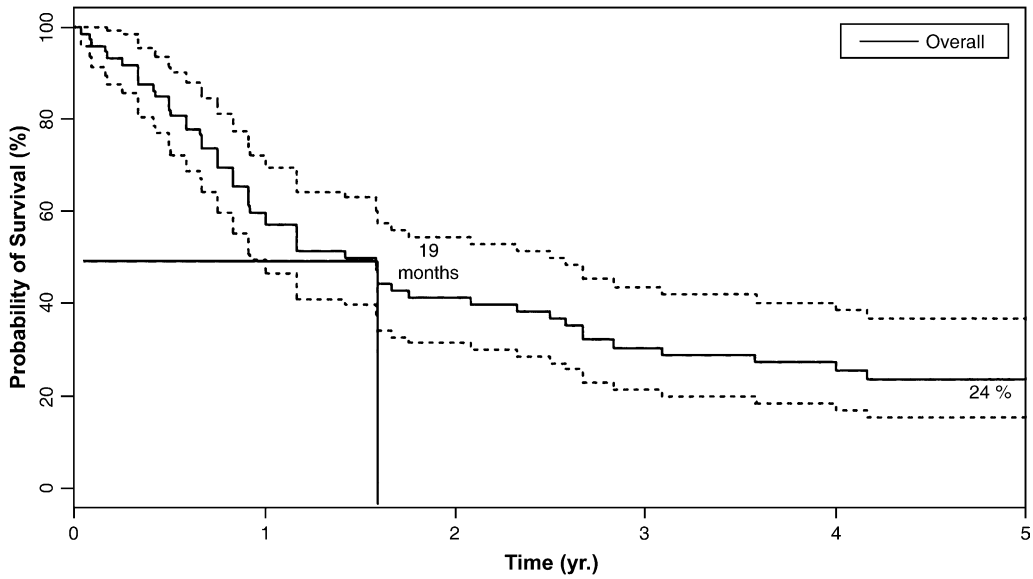

Fig. 1. Overall survival. Median overall survival was 19 months, and 5-year survival was 24%.

cannot routinely be directly imaged. In our study, a small bowel follow-through was obtained in 60 percent of the patients and had a specific diagnostic value of 65%. An abdominal CT was useful in the detection of advanced disease twice as frequently (34%) compared to diagnosing the primary tumor. The diagnostic tool of choice should be tailored to the tumor location. Extended upper endoscopy and push endoscopy can visualize proximal jejunal tumors, but a small bowel follow-through or enteroclysis are the procedures most likely to diagnose cancers of the distal jejunum and ileum. Although our extended upper endoscopy and enteroclysis results were of limited diagnostic value, they reflect the technical limitations of these tools. Push enteroscopy can usually visualize 40–60 cm of jejunum beyond the ligament of Treitz. Any tumor that is distal to this limit will be hard to detect endoscopically.[16] Newer technology such as capsule endoscopy may help in the diagnosis of small bowel

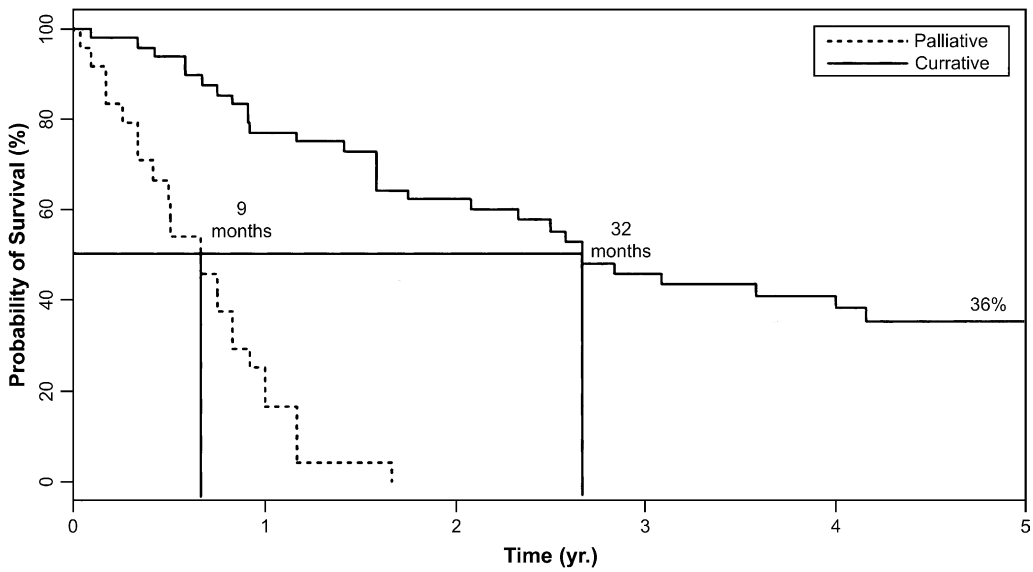

Fig. 2. Curative vs. palliative resection, patients survival. Patients who underwent curative resections had a median survival of 32 months, which was statistically longer compared to the palliative treatment group, who had a median survival of 9 months ($P < 0.0001$).

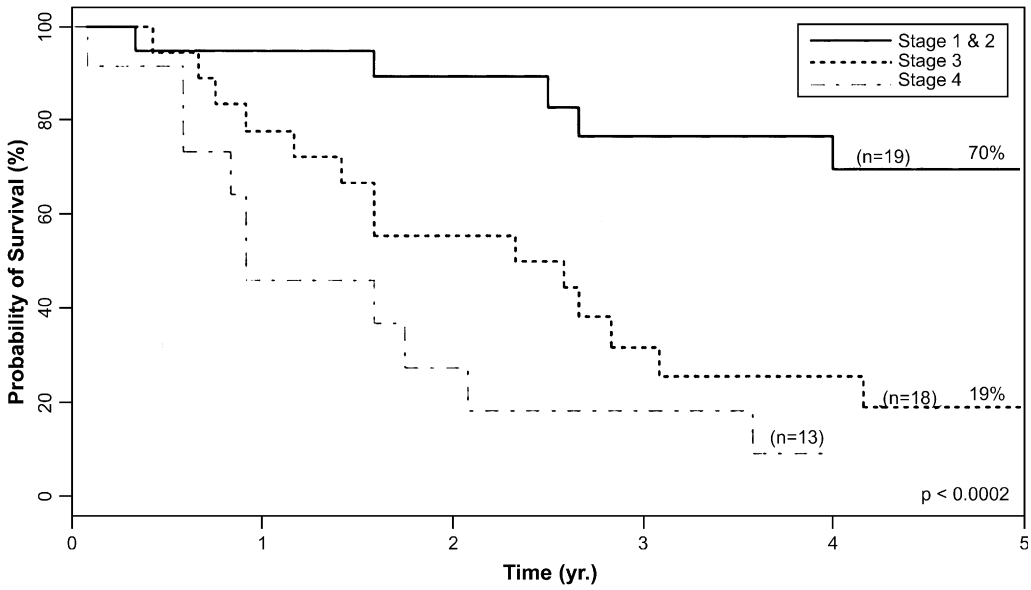

Fig. 3. Survival by tumor stage. Because there was only one patient in stage I, stage I and II patients were combined. Stage of the disease was found to be a statistically significant factor for survival in multivariate analysis ($P<0.0001$).

ACA, but limitations in its use include potential capsule retention with stenotic cancers.[17] More invasive approaches such as diagnostic laparoscopy or laparotomy with intraoperative endoscopy can also be useful in the diagnosis of small bowel malignancies when the diagnosis is suspected clinically.

The lack of proven efficacious adjunctive therapies leaves early diagnosis, plus an aggressive surgical approach, as the most effective treatment for small bowel ACA. In our series, half of the patients had distant metastasis at the time of diagnosis, demonstrating the insidious onset and aggressive natural history of this disease. Although these findings can be interpreted as a result of referral bias, tumor-free resection is still critical for long-term survival. Due to anatomic considerations, jejunal and ileal ACA demand a different surgical approach than their duodenal counterparts. To obtain adequate surgical margins for proximal duodenal adenocarcinomas (first and second portions), pancreaticoduodenectomy is necessary, whereas a segmental resection for the distal (third and fourth portions) tumors is often adequate treatment. Our recent experience with duodenal cancers showed 5-year survival of 54%, with similar results for both pancreaticoduodenectomy and segmental resections performed according to these anatomic considerations.[18] Segmental resection should be sufficient for any jejunal or ileal adenocarcinoma when a curative resection is feasible. In our study, the 5-year survival for the curative patient group was 36%. Because of advanced disease presentation and subsequent poor long-term patient survival with jejunal and ilial ACA, it has been concluded that distal small bowel lesions obstruct later than proximal ones.[2] The most prevalent identifiable risk factor in this study was Crohn's disease. Seven of nine patients with Crohn's disease had ACA of the ileum in agreement with previous reports of ACA and Crohn's disease.[19–20]

Sixty-six percent of patients who had an operation with curative intent developed recurrent tumors, a clear indication of an aggressive tumor biology. A systemic complaint, namely weight loss, was an independent poor prognostic factor for patient survival. Not surprisingly, higher stage of the disease correlated with the poorer outcomes. Postoperative medical therapy has not been adequately investigated for jejunal and ileal ACA. In our study, the inconsistent and uncontrolled use of multiple chemotherapeutic agents prevents any conclusions about the benefit of their use. Traditional postoperative adjuvant chemotherapy regimens designed for colon cancer have not been proven beneficial for small bowel ACA patients. A review of the National Cancer Database by Howe et al.[21] found similar results in a patient population where one third of patients had chemotherapy. Newer, more effective drugs (in particular, irinotecan and oxaliplatin) have been used infrequently in the management of small bowel ACA.[22] The lack of evidence for effective chemotherapy

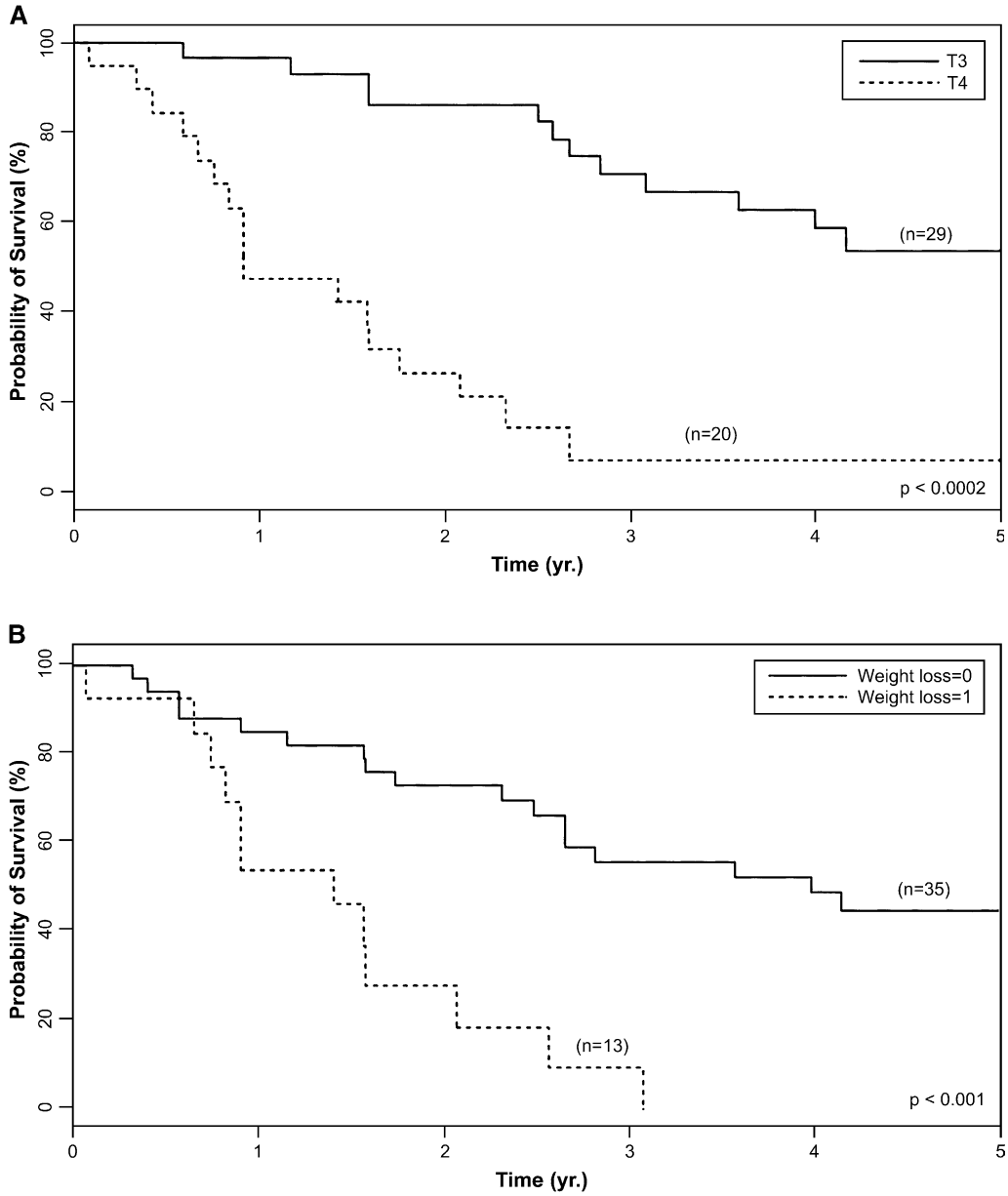

Fig. 4. Survival by (A) tumor depth of invasion and (B) weight loss: Tumor depth of invasion, as with T4 lesions, and weight loss were poor prognostic indicators in the univariate analysis. In multivariate analysis, weight loss maintained significance, whereas a T4 cancer was not a statistically significant indicator.

makes physicians reluctant to routinely offer postoperative therapy for patients with small bowel ACA.

CONCLUSIONS

Adenocarcinoma of the jejunum and ileum is a rare disease that is commonly diagnosed at an advanced stage. Early recognition requires clinical suspicion and diligent examination including evaluation of the small bowel. Improved surveillance and exhaustive diagnostic tests should be considered in selected patients, such as those with occult blood loss or a predisposing risk factor, such as Crohn's disease. We identified weight loss, stage, and tumor recurrence as independent poor prognostic factors. In our experience en bloc segmental resection was the only effective treatment. Adjuvant chemotherapy is unproven at present, although colorectal chemotherapy is often recommended. The genetic abnormalities and identification of markers of biological behavior for small bowel ACA need to be delineated before the application of targeted therapy will be feasible.

Table 4. Published results for adenocarcinoma of the jejunum and ileum

	Patients (n)	Jejunal/ileal distrubution (n)	Curative resection (n)	Stage (I,II,III) n (%)	Stage (IV) n (%)	Predictors of survival	Overall survival (mo)	Curative resection survival (mo)	Overall 5-year survival (%)
Bauer et al.[12]	16	11/5	9	9 (56)	7 (44)	LN positivity	17/10[a]	NA	0/25[a]
Veyrieres et al.[13]	50	36/14	NA	NA	NA	Anemia	NA	NA	59/62[b]
Cunningham et al.[4]	16	10/6	NA	NA	NA	NA	13[c]	23[c]	NA
Howe et al.[21]	1528	880/648	1381	NA	NA	Age, tumor site, curative resection stage	19.7	29/31[a]	38/39[a]
Ito et al.[7]	26	14/12	26	NA	NA	Tumor (T) LN stage	NA	36.5[c]	26[c]
Dabaja et al.[15]	82	54/28	NA[d]	NA	NA	Curative resection LN positivity	26	NA	30
Present study 2004	77	52/25	50	38 (49)	39(51)	Curative resection Recurrence Weight loss	19	36	24

[a]Overall survival separated by jejunal and ileal distribution.
[b]The numbers represent actuarial survivals by jejunal and ileal tumor locations.
[c]Numbers presented in this study include duodenal tumors as well.
[d]Only 83% of the patients had an operation; the number of curative procedures is unknown.

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