J Gastrointest Surg (2008) 12:2051–2056
DOI 10.1007/s11605-008-0740-3

Evolution of a Surgeon: A 40-Year Perspective

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Received: 14 October 2008 / Accepted: 14 October 2008 / Published online: 30 October 2008

I have looked forward to this day with anticipation and some trepidation for nearly 2 years. When I first joined the SSAT, about 30 years ago, I was then and am now in awe of the SSAT, and for me it has never lost its luster. When I was inducted, some of the founders were still active, providing me with special memories of those early days, and over the years, I have made many friends and acquaintances through my involvement in the SSAT. In a sense I grew up in this organization.

Several SSAT members have served as role models for me over my career and as such were my heroes: Wally Ritchie, Frank Moody, and Bill Silen come immediately to mind. Each in his own way was a help to me, willing to provide advice, support, or encouragement for a young surgeon trying to understand the traditions and pitfalls, as well as the opportunities of academic surgery. Other SSAT members who have contributed to my professional development include Ted Copeland, Joe Fischer, Stan Dudrick, Bernie Jaffe, Lou Flint, Jim Thompson, Isidore Cohn, Tom DeMeester, and the late Jim Thompson, to name just a few. And I cannot fail to mention Larry Cheung and Bing Rikkers, Frank Moody's disciples in their Utah days, who were always good comrades.

My last words of appreciation go first to Dr. Eugene Jacobson. Gene, when he was the first Professor and Chairman of Physiology at the new University of Texas Medical School in Houston, took me into his GI laboratory, despite the fact that I was a surgeon, and turned a neophyte into a fairly competent investigator. I understood that I would never win a Nobel Prize, but he managed to train me well enough for me to be awarded several NIH ROI grants, a good start to any young surgeon's career. For that I thank Gene and also Wally Ritchie who first whetted my appetite for bench research during my time at the Walter Reed Army Institute of Research.

Last, but not least, I want to recognize Dr. John Ochsner who recruited me to the Ochsner Clinic in 1976 and who has served ever since as my role model, mentor, and friend. John is truly one of the great surgeons of the twentieth century. I have been very lucky to follow behind a man of such extraordinary ability, character, and commitment to surgery and to his patients.

Speaking of research and great surgeons, I recently ran across these words: "…the achievement of the surgeon and his assistants becomes one of the greater glories of science… in the operating room all results of the most

This article was perviously published without the photograph of Dr. Bowen in Journal of Gastrointestinal Surgery Volume 12, Number 10 (October 2008). It is reproduced here in its entirety.

Presidential Address at the annual meeting of the Society for Surgery of the Alimentary Tract, San Diego, CA, May 19, 2008.

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improbable reaches of research, all the immense accumulation of medical knowledge are drawn upon in a determined drive towards… preservation of one human life."[1]

Those words were written in an article that appeared in *Time Magazine* on May 3, 1963 entitled, "The Best Hope of All." A few months later I entered medical school and, perhaps naively, began a quixotic journey to become a doctor. The article in *Time* was written to extol the new "modern surgeon" who pursues knowledge to establish a scientific foundation for surgical treatment and who dares to perform procedures so radical that they were almost unimaginable a few years before. In the same article Dr. Donald Effler, the Cleveland Clinic surgeon, was quoted as saying, "A great surgeon must have a fierce determination to be the leader in his field. He must have a driving ego, a hunger beyond money. He must have a passion for perfectionism." The surgeon luminaries of the twentieth century, including many of our predecessors in SSAT, possessed powerful personalities and fierce determination in order to achieve success and to further the development of surgery. Throughout most of the twentieth century, the image of a surgeon was that of a commanding presence, capable of controlling all facets of patient care, a leader the Germans called a *geheimrat*. Advances required strong personalities with great self-confidence, ego strength, and limitless perseverance.

Today the surgeon's image is changing as a result of many factors—social, organizational, legal, economic, and political. For the most part, these forces are beyond the control of the surgeon. Today's surgeon, of necessity, must fit in with a team of health care professionals and interact collegially with them to be successful.

Becoming a part of a team with other specialists has made it impossible for a surgeon to fulfill the traditional role of "master of the ship." It's acknowledged that a surgeon should understand and be aware of every aspect of his patient's disease and care, but in fact, many others play important roles and make it impractical to retain complete control over the patient's care.

Nevertheless, it is the surgeon who stands before the patient and draws up the contract that permits the surgeon and the team to embark on a plan to correct a surgical problem. And it is the surgeon to whom the patient has entrusted his life and welfare.

Surgeons understand the human cost of failure better than any other professional group in our society. We know that the only thing that really counts is results, i.e., solving a problem with the least cost of human suffering and with optimal benefit to the patient. The commitment to surgery is the defining event for the patient and for the surgeon. Style and artifice are useless if not effective; and founts of knowledge and intellectual speculation are useless unless at the defining moment they provide clarity, thought, and direction to guide the surgeon's hand.

A new distraction is now foisted on a surgeon as a result of rapid communication. The nearly instantaneous spread of new ideas, not only to the medical community but also to the public, brings pressure on the contemporary surgeon to wade through a morass of information, released unedited and untested into the public awareness. The pressure to be *au courant*, to know the latest claims and counterclaims, and to be able to discuss them with the next patient who walks in your office can be a demanding exercise. So much of what is available to the public is, at best, half-baked, sometimes untrue, and often misunderstood to the point it can become a major impediment to winning a patient's confidence. Unfounded claims can create unrealistic expectations that do not account for the full range of possible outcomes and make obtaining informed consent difficult. The public is ill-equipped to evaluate medical information, prioritize its importance, and make rational decisions.

As surgeons, we cannot become deluded by claims of what could or should be, and as surgeons we face our own stern realities in which events may unfold unpredictably and absolute control is an illusion. This reality now blends into today's world where statistics, algorithms, and consensus opinions tell us what others say we should achieve. This places pressure on every surgeon to be risk averse. Unfortunately, many problems we face are complex, their solutions involve risk for both the patient and the surgeon, and statistical probabilities are not always achievable. We struggle to deal with outsiders from the secular world who want to control and quantify the unquantifiable, thus deterring performance and inhibiting innovation. How and if this tension can be resolved remains an open question.

Managers in today's world believe process and controls produce a better product. I suppose it was just a matter of time until the "organization man" that we derided in the 1960s and 1970s turned his managerial skills toward the unbowed world of medicine. This raises the question whether surgeons have to become subservient to the organization man to survive. Will "best practices" and treatment "guidelines" retard innovation and produce mediocrity or will they provide a constructive framework for producing better outcomes? Standardization of routine processes insures safety from technical and administrative errors, to be sure. Computer programs have already improved our ability to collate information and to track and coordinate patient care. However, fear of intrusive oversight and misuse of information can create a "gotcha" mentality that will produce a chilling effect on surgical decision making. Information that can be manipulated against anyone who dares to challenge orthodoxy confers unfettered power on the organization man. Fear breeds

temerity, a surgeon's enemy when there is a need to make decisions, act with partial information, or to use experiential judgment.

Where then will the surgeon leaders of the twenty-first century come from? Will they be as talented, imaginative, and determined as the personalities attracted to our profession in the past? Are these types needed or even wanted in the new world order? In her book *The Scalpel's Edge*,[2] Pearl Katz opines that the new surgical heroes may be those who admit doubt and uncertainty, communicate sensitively with patients in an effort to have patients participate in decision making, communicate openly with their colleagues, and take risks not for their patients but with their patients. Katz's vision of the surgeon's role in the future, as seen through the eyes of a cultural anthropologist, bespeaks a humanistic adaptation that is already underway. It appears that the boldness and rugged individualism that characterized so many of our surgeon pioneers will have to be sublimated and further modified for the next generation of surgeons to be effective leaders.

The technological explosion in American surgery began in 1989 when the application of the laparoscope to cholecystectomy was proven to be not only doable but teachable to thousands of trained surgeons. Its advantages over standard surgery caused a stampede to learn the technique.

In my case, I saw two laparoscopic cholecystectomies performed in a small community hospital in early 1990. And within a few weeks, I had performed my first laparoscopic cholecystectomy, having cobbled together the rudimentary equipment. This was as close to see one, do one, teach one as it gets. From that experience, I developed renewed respect for our pioneering predecessors who performed much more risky procedures with even less guidance under even more primitive conditions. Because it could be performed by thousands of surgeons hundreds of times and because it is so perfectly amenable to minimally invasive techniques, laparoscopic cholecystectomy did more, in my opinion, to advance all of surgery, and especially gastrointestinal surgery, than any other surgical innovation in my professional life.

The parallel development of small, modular, digital computers was a fortuitous congruence that led visionaries to see the great potential created by combining minimally invasive surgery with the power of computerized control. The impact of these developments is so far reaching that they have truly created a new paradigm affecting every aspect of modern surgery. A partial list of impacted areas would include training, workforce requirements, facilities, economics, levels of specialization, certification and credentialing, litigation, reimbursement patterns, and not the least affected—patients' expectations.

Nevertheless, the technological developments of the past 20 years, while providing a thrust to the future of surgery that I never dreamed of, have produced a host of complex problems. Among those concerns is the future of general surgery. As early as 1991, in the title of his SSAT Presidential address, William Silen implored, "Where Have the General Surgeons Gone?"[3] He presciently predicted that as the number of specialists and consultants increase, costs would escalate, rapport with the patient and trust in the physician would erode, malpractice litigation would escalate, and college students' interests in medical careers would wane. Have not all of his predications come to pass?

The extent of the threat to general surgery as a specialty began to come into focus just as the new millennium began. The AMA Physician Database showed a decline of just over 2,600 general surgeons in 4 years, a fall in absolute numbers from 27,509 in 1998 to 24,902 in 2002. This occurred despite a population growth in the U.S. of approximately 25 million each decade since 1970. Concomitantly, the production of general surgeons in the U.S. over the past 25 years has been remarkably constant at an even 1,000 per year. This has continued through the match in 2007 when over 99% of 1,055 positions were filled.

There are two significant and relevant demographic factors that are noteworthy, although their impact on the future of general surgery is uncertain. The first is that in 2001 the percentage of positions filled by U.S. medical school graduates fell below 90% for the first time in history.[4] And in 2007 the percentage filled by U.S. graduates fell below 80%. This pattern is not universal for all specialties. For example, anesthesiology trends are the reverse, having filled only 30% of their slots in 1996 (their nadir) and increasing dramatically to 98% filled with 78% U.S. graduates in 2007. Likewise, diagnostic radiology filled only 50% in 1996 compared to 100% in 2007 with 89% U.S. graduates. Clearly, there is a declining interest in general surgery and its related specialties among U.S. medical graduates.

The second demographic of note is that women now comprise over 50% of medical school graduates. And, there has been a drop of over 50% in the total number of men applying to medical school since 1974. Bucking these trends, general surgery remains a white male dominated specialty with little more than 20% being females. The gender factor is widely assumed to have a negative impact on the surgical workforce by limiting the available candidates for residency because of lifestyle issues and by reducing the availability of practicing general surgeons due to a greater likelihood of women choosing to interrupt or shorten their careers.

These data augur for a further decline in the general surgery workforce that will limit available candidates for further specialty training. Because the number of federally funded entry positions in general surgery is capped by the

Balanced Budget Act of 1997 at about 1,000 per year, competition for candidates to fill subspecialty slots will be fierce. And, it is not surprising that several specialties have already successfully petitioned the American Board of Surgery to allow them to accept candidates after only 3 or 4 years of general surgery training.

But what explains the actual decline in the number of practicing general surgeons that is already occurring? Dr. David Cosman, a practicing vascular surgeon in Los Angeles, writes an opinion column in *General Surgery News* expressing his views on a wide range of subjects including medical economics, politics, practice, and the future of surgery. He recently opined that "there is a rising tide of physician dissatisfaction in this country…. Demoralized by decreased reimbursements, endless regulatory rituals, useless compliance exercises, and a distrustful patient population, physicians are on the ledge, and it won't take much more to push them over the edge."[5]

This sentiment is shared by more and more practicing surgeons who don't see a way out of the quagmire they find themselves in. Reimbursement for surgical services in real dollars is approximately 30% of what it was 15 years ago, and yet practice overhead has more than doubled largely due to inflation, regulatory mandates, rising insurance premiums, and administrative cost increases. In a statement to a senate committee this year (Senate Committee on Health, Education, Labor and Pensions, February 12, 2008) the American College of Surgeons, addressing health care workforce issues for the future, concluded that "the single most important factor shaping the surgical workforce issue is declining reimbursement." These concerns beg the question of whether it is too much to ask that present and future surgeons have some hope of prosperity and security. Is it any wonder that more and more general surgeons are either retiring early or seeking another career?

One thing is certain; the workforce is declining as the American populace grows larger and older. These kinds of trends take decades to produce and decades to reverse. Unfortunately, there is no plausible evidence to suggest that the public or our elected officials perceive a physician shortage or, more specifically, a shortage of surgeons. The exceptions to this reality are limited to rural areas that have little or no service and lack the political influence to affect public policy. Surgeons need formidable public relations and formidable political advocacy to stabilize and hopefully improve reimbursement. So far, as a profession, we have not developed effective political representation, and, unfortunately, we have no natural allies to champion our cause. Alone we have little political leverage. This is not a condemnation of our surgical societies, all of which were founded for educational, not political purposes. Furthermore, traditional professional societies may not be the best means through which to achieve political influence. Yes, the American public does think there is a health care crisis, as the media and opinion polls remind us daily, but the concern of the American public is solely about their individual cost and their access to care, not surgeon's pay and lifestyle.

On the production end of the equation, general surgery residency numbers remain constant for now only because the number of international applicants remains robust. Basically, surgery positions fill with qualified U.S. applicants and then top off with qualified foreign graduates. The decline in U.S. seniors choosing careers in surgery augurs poorly for the future, and the increasing reliance by American training programs on foreign medical graduates to fill positions makes the continued supply of surgical specialists tenuous.

This concern, first brought to prominence by the 2001 general surgery match results, has been the subject of much discussion. After reviewing dozens of articles written about the disaffection of graduating seniors for general surgery, and after trying to digest reams of demographic data, it seems fairly transparent to me: Today's contemporary generation (or Generation X, defined as anyone born after 1965) is not as attracted to general surgery (or its subspecialties) because they see in them less relative value as compared to other specialties and other professions. The simplistic explanation has been to blame "lifestyle issues." This catch phrase implies that the younger generation is not as committed or as willing to work as previous generations. The notion that if surgeon educators could just make surgical training more attractive and user friendly, and things will get better, is frankly naive. Maybe some medical students have been scared off because they see how long and hard surgeons work or how stern and demanding they can be at times. Clearly, some react negatively to the surgical ethos. Unfortunately, the cause of disaffection is much deeper and not so easily corrected.

One important influence on a career's attractiveness is financial. A former medical director at the Ochsner Clinic said, "when someone says it's not about the money, it's the principle of the thing, it's always about the money." Professor Michael Porter of the Harvard Business School, at this year's annual meeting of the American Surgical Association,[6] characterized health care as a "zero sum competition", meaning that all the participants in the healthcare community are pitted against each other to carve out more value at the expense of others. Therefore, is it any wonder that the next generation is questioning commitment to a specialty whose status has become financially compromised and whose services, especially in general surgery, have been, I think, intentionally devalued? Isn't fair compensation a reasonable expectation for years invested in a surgeon's education, for the stresses and interruptions in family life, and for a life of commitment to

the frailties of others? How can anyone expect to have balance in their life if they are chronically overworked and financially strapped?

Fortunately, there are still highly motivated and talented candidates who are willing to pay the price necessary to be molded into what is one of the most personally rewarding professions that exists, that of a surgeon. The intangible rewards are still among the most satisfying of any profession I know. But the reality is that the life of a surgeon is not easy and it's not always possible to plan your practice around your personal life. It would be misleading to promise surgical candidates a rose garden. I would much prefer to train young surgeons with realistic expectations, committed to a life of professional attainment and responsibility, than to do anything to weaken the fabric of our profession. And it is incumbent upon those of us in leadership roles to make certain that we stand steadfast against any attempts to compromise or minimize the requirements necessary to become a surgeon. If we overreact to a few poor years in the match and if we begin to undermine the basic tenets of surgical education that have been shown to be tried and true for over 100 years, we will do a lasting disservice to future generations.

We, in our professional capacity, can do very little to change the practice environment that is eating away at so many of our colleagues. The forces producing practice dissatisfaction are, for the most part, beyond our control and reflective of political and societal ills that will require a sea of change to rectify. But, we can take seriously and responsibly our stewardship of the next generation of surgeons. To that end, we must protect the depth and breadth of surgical experience as the bedrock of training.

The science of experience teaches us that mastering most complex human endeavors requires a minimum of 10 years' experience. Surgeon educators have and will continue to develop new methods to teach complex subjects, but there is a limit to how fast the human mind can absorb large quantities of information, synthesize it, and apply it to an almost infinite number of circumstances. Furthermore, training parameters must be designed to adequately train the slowest, not just the quickest and most facile. When dealing with human life we are obligated to maintain training goals that aim, as in aviation, for zero defects. In medicine, in contrast to other professions such as civil engineering, solutions to urgent and complex problems must be acted on in real time, often with partial information. Surgeons must be trained to manage the worst scenarios and to confront the unexpected. The human condition comes in limitless variations, making it essential that each surgeon has the capacity to respond flexibly and reflexively. Professional discipline and technical skills are gained through long hours of repetition and through struggling under adverse circumstances. William Halsted and other great surgeon educators of the twentieth century understood and stated explicitly that it takes time and years of experience to train a surgeon.

It is popular today to appear flexible and understanding. But in my 40 years in surgical education, as a trainee or trainer, I can see no justification for being anything but demanding and rigorous in the design of the training process. In surgery, the only acceptable performance goal is the best that can be achieved for each and every patient. Nothing less is acceptable. This can only be accomplished if each surgeon is broadly and expertly trained and experienced.

While 10 years is probably a minimum required to achieve expertise in most complex fields, including surgery, more and more experience alone is not a guarantee of success. Gaining experience is only the starting point. Anders Ericsson, the editor of the *Cambridge Handbook of Expertise and Performance*,[7] states, "The number of years experience in a domain is a poor predictor of performance." This observation is particularly relevant to the experienced and mature surgeon. Ericsson holds that rather than through more and more experience, sustained performance is achieved through what he calls "dedicated exertion", i.e. repeatedly practicing the most difficult tasks that lead to excellence and consistent performance. If a task gets easy and the mind wanders, routine tasks may be executed mindlessly and mistakes occur.

A recent study from Harvard, for example, reported the causes of surgical technical errors that had resulted in malpractice claims.[8] The majority (or 73%) involved experienced surgeons, and 84% occurred in routine rather than advanced procedures requiring special training. Therefore, successful performance requires more than experience or "time in grade" in U.S. Army jargon, but continuing focus on decision-making and constant awareness in routine operations for the occurrence of complex circumstances.

The importance of experience in training leads me to a few thoughts on the design of surgical training in the future. You have already deduced that I am "old school." That I feel surgical training must be, of necessity, long enough and rigorous enough for the trainee to acquire not only practical experience but also to acquire intangibles like mental and emotional discipline. In my opinion, early specialization after only 3 years of general surgery, as has been proposed,[9] will produce a surgical workforce of narrowly trained specialists who lack the foundation, maturity, and breadth of experience to meet the challenges they will surely confront in their careers. If the perceived disaffection of senior medical students is used as a reason to reduce the rigor of general surgery training prior to specialization in an attempt to make surgery more alluring, it will severely diminish the effective workforce of qualified general surgeons. An unintended consequence will be to create several tiers of qualification and credentialing that will be a

nightmare to administer and unravel. Credentialing committees will be forced to rely on formulas to determine competency, moving standards toward the lowest common denominator. Litigation over qualifications will ensue, producing a morass that the courts are ill prepared to adjudicate. Gaps in coverage of specific conditions will emerge, and hospitals, as they become increasingly reliant on fragmented specialists, will have to enlarge their staffs to maintain continuity of care.[10] Who will be empowered to convene the specialists to assign ultimate responsibility for the whole patient? I fear that into this void will lead an opportunist, perhaps with little or no surgical experience, to seize the role of ringmaster. All of this will magnify the anticipated workforce shortages, and the redundancy of specialists will lead to rising costs. In the end, continuity of care will be sacrificed and patients will suffer.

Thirty-five years ago a Yale psychologist, Irving Janis, published an essay in the *Yale Alumni Magazine* to explain how a group of intelligent people working together to solve a problem can sometimes arrive at the worst possible answer.[11] He called his radical new theory "group think." The consequences of such an error can be devastating. A minor consequence would be that a proffered solution simply delays resolution of a problem. More serious consequences can lead to tragic outcomes such as the Bay of Pigs fiasco, the escalation of the Vietnam War, or now, the prosecution of the Iraqi War.

Today, group think is studied in military colleges, political science classes, business schools and academia. In response to criticism regarding decisions leading up to the Iraqi War, the CIA announced it has initiated new procedures to minimize the risk of "group think." John A. Kringan, head of the CIA's Directorate of Intelligence, has outlined new procedures setting up "alternative analysis" teams to guard against decisions going off in the wrong direction for the wrong reasons. This process provides for an external authority to test the assumptions and conclusions of the group before potentially damaging or irreversible action is taken.

My concern is that the future of surgical training, its basic premises and format, be examined and debated, and any proposed changes subjected to the equivalent of an alternative analysis before anything is done that could permanently weaken the foundation of surgery in America. A minimum of 5 years of surgical training before specialization should be retained as a foundation until all the consequences of compressed general surgery training have been explored.

Tomorrow's surgeon is faced with mastering more knowledge, not less; more complexity, not less; and the hard-earned lessons of the past must be passed on to the next generation. It is crucial that we shape the scope of knowledge and experience that will be required of future surgeons and that we not be unduly influenced by transitory exigencies. In the end we cannot control all the forces buffeting our society, but we can and should control the fundamental qualifications necessary to fulfill our responsibility to the future of our profession. And above all, we must instill in future surgeons, in Dr. Effler's words, "a passion for perfectionionism." Nothing less will do.

"Be not the first by whom the new are tried

Nor yet the last to lay the old aside"

Alexander Pope

Essay on Criticism, 1711

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J Gastrointest Surg (2008) 12:2057–2065
DOI 10.1007/s11605-008-0684-7

Zenker's Diverticula: Feasibility of a Tailored Approach Based on Diverticulum Size

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Received: 31 May 2008 / Accepted: 20 August 2008 / Published online: 23 September 2008

Abstract
Background Zenker's diverticula (ZD) can be treated by transoral diverticulostomy or open surgery (upper esophageal sphincter myotomy and diverticulectomy or diverticulopexy). The aim of this study was to compare the effectiveness of a minimally invasive (group A) versus a traditional open surgical approach (group B) in the treatment of ZD.
Material and Methods Between 1993 and September 2007, 128 ZD patients underwent transoral diverticulostomy (n=51) or cricopharyngeal myotomy and diverticulectomy or diverticulopexy (n=77). All patients were evaluated for symptoms using a detailed questionnaire. Manometry recorded upper esophageal sphincter (UES) pressure, relaxations, and intrabolus pharyngeal pressure. The size of the pouch was measured on the barium swallow. The choice of treatment was based on the size of the diverticulum and the patients' preference. Long-term follow-up data were available for 121/128 (94.5%) patients with a median follow-up of 40 months (interquartile range, 17–83).
Results Mortality was nil. Three patients in group A (5.8%) and ten in group B (13%) had postoperative complications (p=n.s.). Hospital stays were markedly shorter for patients after diverticulostomy (p<0.01). Postoperative manometry showed a reduction in UES pressure, improved UES relaxation, and lower intrabolus pressure in both groups (p<0.05). Four patients in the open surgery group (5.2%) complained of severe dysphagia after surgery (three of them required endoscopic dilations). In the transoral diverticulostomy group, 11 patients (21.5%) required additional septal reduction (n=8) or a surgical myotomy (n=3) for persistent symptoms (p<0.01); nine of these 11 patients had a ZD≤3 cm in size. After primary and complementary treatments, symptoms disappeared or improved significantly at long-term follow-up in 93.5% of patients in group A and 96% of those in group B.
Conclusion Diverticulostomy is safe, quick, and effective for most patients with medium-sized ZD, but open surgery offers better long-term results as a primary treatment and should be recommended for younger, healthy patients, especially those with small diverticula. Small ZD may represent a formal contraindication to the transoral approach because an excessively short septum prevents a complete division of the sphincter fibers.

Keywords Zenker's diverticulum · Transoral diverticulostomy · Myotomy · Diverticulectomy

Introduction

Cricopharyngeal diverticula are protrusions of pharyngeal mucosa through an area of relative weakness in the

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posterior wall of the pharynx, limited laterally by the oblique fibers of the thyropharyngeal muscle and inferiorly by the inferior constrictor muscular sling, the so-called Killian's triangle[1]. A higher hypopharyngeal pressure during swallowing and a lower resistance of the posterior wall of the hypopharynx are fundamental factors in the pathogenesis of cricopharyngeal diverticula—also known as Zenker's diverticula (ZD), from the German pathologist who first described the condition[2].

The lower part of the inferior constrictor muscle is a distinct anatomical entity known as the "cricopharyngeal muscle," which, together with the muscle fibers encircling the upper esophagus, forms the upper esophageal sphincter (UES), which is tonically contracted at rest and relaxes on swallowing. The role of abnormal UES relaxation in causing excessive intrapharyngeal pressures during swallowing was clarified by manometric and cineradiographic studies nearly 60 years ago.[3–7] Since then, UES myotomy, to ease the functional obstruction, has become an essential part of surgical treatment for pharyngeal diverticula, together with excision or pexis of the pouch.[8]

Recent developments in minimally invasive surgery have led to endoscopic-stapling devices being used to divide the septum between the esophagus and the pouch to relieve the outflow obstruction at the pharyngoesophageal junction. This alternative endoscopic approach was introduced by Collard in 1993: The anterior wall of the diverticulum and the posterior wall of the esophagus are divided and sealed using an endostapler inserted through a specially designed endoscope (the Weerda diverticuloscope), thus preventing leakage, mediastinitis, or bleeding.[4] This procedure rapidly became widespread and is now often considered the treatment of choice for cricopharyngeal pouches.[9–11]

In 2003, in a relatively small series of patients, we showed that diverticulostomy was safe, quick, and effective for most patients with medium-sized ZD but that open surgery offered better long-term results and should be recommended for younger, healthy patients with small or very large diverticula.[12] The present study thus aims to expand on our experience of treating ZD with both techniques, basing the choice of treatment on the diverticulum's size.

Material and Methods

Patient Population

All patients with ZD referred to our surgical unit between 1993 and September 2007 were included in the study.

Patients were assessed for surgical risk and graded from 1 to 3 according to the risk scale of the American Society of Anesthesiologists (ASA).

Symptom Assessment

Patients' symptoms were recorded using a standard questionnaire for upper foregut diseases. Dysphagia and regurgitation (the most common symptoms of pharyngeal diverticula) were scored according to severity and frequency. The symptom score was the sum of the severity scores for each symptom (0=none, 2=mild, 4=moderate, 6=severe) and their frequency (0=never, 1=occasionally, 2=once a month, 3=every week, 4=twice a week, 5=daily); the highest score obtainable was 22. Other symptoms (heartburn, sialorrhea, etc.) were assessed but not counted in the symptom score.

Respiratory symptoms (cough, episodes of pneumonia per year, and asthma) were also recorded.

Diagnostic Studies

Barium Swallow The diagnosis of pharyngoesophageal diverticula was confirmed by a barium swallow, and the size of the diverticulum was measured in a lateral projection as the distance from the neck of the diverticulum to the bottom of the pouch.

Endoscopy Upper gastrointestinal endoscopy was performed under mild sedation using a flexible scope to rule out any concomitant anomalies in the esophagus or stomach and, if the diverticulum interfered with the placement of the manometric tube, to pass a guidewire for the manometric probe.

Esophageal Manometry This was performed using instruments and a technique described in detail elsewhere.[13] Briefly, an eight-lumen low-compliance infused system with computerized data acquisition and analysis was employed. A high-frequency data acquisition mode (50-Hz) was used to record the rapid events occurring during swallowing. UES pressure was measured, while the catheter was withdrawn at a constant rate of 5 mm/s. The maximum amplitude recorded by each probe during its passage through the UES was averaged and considered as the UES pressure.

To evaluate pharyngoesophageal function during swallowing, the manometric probe with four radially oriented side holes was positioned at the upper edge of the UES, with two other side holes situated 5 and 10 cm above (in the distal and proximal pharynx, respectively) and one situated 5 cm below the UES (in the cervical esophagus). Ten swallows of 10 ml of water were evaluated, considering the following pharyngeal contraction parameters: amplitude, duration, and intrabolus pressure, i.e., the pressure generated by the passage of the bolus in the distal pharynx and seen at manometry as a slow pressure increase (shoulder) before the major upstroke generated by contrac-

tions of the pharyngeal wall, as described by Cook et al.[5] We recorded the number of complete UES relaxations (expressed as the percentage of UES relaxations with a residual swallowing pressure <10 mmHg) and the coordination of UES opening with pharyngeal contractions (expressed as the percentage of relaxations with the nadir of the UES pressure coinciding with the pharyngeal wave's major upstroke).

Treatment of Zenker's Diverticula

From January 1993 onwards, two options were available for treating patients with ZD: (a) endoscopic diverticulostomy with a stapler or (b) open surgery for UES myotomy with or without diverticulectomy. Both procedures were performed under general anesthesia with endotracheal intubation. Informed consent was routinely obtained from all patients.

Endoscopic Diverticulostomy With the patient supine and the neck extended, a Weerda diverticuloscope (Karl Storz, Tuttingen, Germany) was positioned with the anterior blade in the esophageal lumen and the posterior blade in the diverticulum. A telescope 5 mm in diameter was passed through the scope. A 30-mm disposable surgical endostapler (Ethicon Endo-surgery) was inserted through the Weerda scope to divide the septum between the diverticulum and the esophageal lumen. One or two stapler applications were used.

UES myotomy This was performed through a left laterocervical approach, anteromedial to the sternocleidomastoid muscle. The diverticulum was isolated, and the cricopharyngeal muscle fibers were divided at the midline posteriorly from the neck of the sac down to the esophagus over a length of 4 cm. After completing the myotomy, diverticula >3 cm were transected using a stapler; diverticula of 1.5 cm or less were left in place; diverticula nearing 2 cm in size were inverted below the pharyngeal muscles and sutured to the muscle layer with two non-absorbable stitches.

Patient Stratification

The endoscopic procedure was suggested for patients with diverticula >3 and <5 cm in length; open surgery was recommended for patients with diverticula <3 or >5 cm. Postoperative course and any adverse events occurring after surgery were recorded.

Additional Procedures A Nissen fundoplication was also performed in three patients with gastroesophageal reflux disease and hiatus hernia; an intrathoracic esophagectomy was performed in one patient for esophageal cancer.

Follow-up Patients had a barium swallow a month after the operation and esophageal manometry after 6 months, when symptoms were reassessed using the same questionnaire, and patients were also asked if they were entirely or partially satisfied or dissatisfied with their treatment. Follow-up was yearly thereafter. Patients who failed to show up at the outpatient clinic were interviewed by phone. A procedure was considered a failure whenever patients complained of persistent dysphagia or (in cases treated with open surgery) recurrent diverticula.

Statistical Analysis

Data were collected in a database and analyzed using commercially available statistical software (Statview; SAS Institute, Inc., SAS Campus Drive, Cary, NC, USA). Data are expressed as medians and interquartile ranges (IQR). The Mann–Whitney and Wilcoxon tests were used as appropriate. Fisher's exact test and the chi-square test were used to compare categorical data, as appropriate. A difference <0.05 was considered statistically significant.

The present study was approved by the local Bioethic Service for human study of the University of Padua.

Results

Clinical Data and Morbidity

During the study period, 128 patients with ZD were referred to our surgical unit: They included 90 men and 38 women with a median age of 66 years (IQR, 59.5–74). Fifty-one patients (38 men and 13 women), a median of 68 years old (IQR 60–75), were treated with endoscopic diverticulostomy (group A), and 77 patients (52 men and 25 women), a median 66 years old (IQR, 59–72), were treated with open UES myotomy (group B), p=n.s. In the second group, myotomy was performed alone in eight patients (10.4%) and combined with a diverticulectomy in 41 patients (53.2%) and with a diverticulopexy in 28 (36.4%). Eight patients explicitly asked for an endoscopic treatment: Four had a diverticulum shorter than 3 cm, one had a diverticulum 3 cm in length, and three had a diverticulum larger than 5 cm.

The main demographic and clinical data on the patient population are given in Table 1. The median symptom score was 13 in group A (IQR, 10–16) and 14 in group B (10–15.5), and symptom duration was 18 months in group A (IQR, 12–36) and 18 months in group B (IQR, 12–24), p=n.s. The presenting symptoms are listed in Table 2. As expected, dysphagia was the most common symptom, followed by regurgitation. Other symptoms included throat

Table 1 Demographic and Clinical Data of the Study Population

	Transoral approach (*n*=51)	Open surgery (*n*=77)	*p* value
Age (years)	68 (60–75)	66 (59–72)	n.s.
Male/Female	38/13	52/25	n.s.
Duration of symptoms (months)	18 (12–36)	18 (12–24)	n.s.
Symptom scores	13 (10–16)	14 (10–15.5)	n.s.
GERD/hiatus hernia	10 (19.6%)	20 (16%)	n.s.
Pneumonia	11 (21.5%)	12 (15.6%)	n.s.
ASA score			n.s.
I	16 (31.5%)	31 (40%)	
II	26 (51%)	40 (52%)	
III	9 (17.5%)	6 (8%)	
Size of pouch	3.5 (3–5)	2.5 (1.5–4)	0.0001

Data are expressed as medians (IQR), as necessary.

lump and throat pain. Recurrent lung infections were reported by almost one in five patients.

In group A, the pouch was a median 3.5 cm in size (IQR, 3–5): Four patients had diverticula shorter than 3 cm (and requested a transoral approach); 21 had diverticula approximately 3 cm long; nine had diverticula between 4 and 5 cm long; and three had diverticula larger than 5 cm (two were 6 cm long, one was 7 cm).

In group B, eight patients underwent UES myotomy alone [they all had diverticula ≤1.5 cm (median 1 cm, IQR, 1–1.5)]. Twenty-eight patients had diverticula approximately 2 cm in size [median 2 cm (IQR, 1.5–3)] and, after the myotomy, their diverticulum was inverted below the pharyngeal muscle layer. Forty-one patients had myotomy plus diverticulectomy for diverticula that were a median 3 cm in size (IQR, 2.5–5).

In the diverticulostomy group, nine patients had an ASA risk grade of 3, and 26 were grade 2; in the open surgery group, six patients were grade 3 and 40 were grade 2. The distribution of the risk did not differ statistically between the two groups (p=n.s.).

The duration of the operation was shorter in the endoscopic group (31 min; IQR, 18–36) than in the open surgery group (80 min; IQR, 61–122; $p<0.05$). There were no deaths in either group. The overall morbidity rate was 10% (13/128 patients), with three patients in group A (5.8%) and ten in group B (13%), p=n.s. The postoperative complications are summarized in Table 3. All the complications in group A patients were due to difficulties encountered in inserting the diverticuloscope or stapler; they included two conversions to open surgery (3.9%) because it proved difficult to expose the septum in one case and a mucosal tear occurred while inserting the endostapler in the other. In group B, there were three leaks, four cases of bleeding with cervical hematoma (requiring surgical drainage in one case), one pericarditis (probably of viral etiology), one transient left recurrent palsy, and one injury to the recurrent laryngeal nerve. Two of the three leaks were detected by the Gastrografin® swallow obtained postoperatively: They were treated conservatively and healed within 2 weeks; one was detected during the operation and was sutured. The hospital stay was shorter in group A (5 days; IQR, 4–5 vs 9 days; IQR, 7–10; $p<0.05$).

Table 2 Presenting Symptoms in 128 Patients with Zenker's Diverticulum

Symptoms	n (%)
Dysphagia	128 (100%)
Regurgitation	118 (78%)
Throat lump	76 (59%)
Heartburn	45 (35%)
Lung infection	23 (18%)
Throat pain	20 (15.5%)

Follow-up and Early and Late Results

An adequate follow-up was obtained in 121/128 patients (94.5%): Of the seven patients lost to follow-up, three (6%) were in group A and four (5.2%) were in group B. Five patients died of unrelated causes. The median follow-up was 40 months (IQR, 17–83) and was similar in the two groups [36.5 months (IQR, 15.5–80.5) vs 41 months (IQR, 18.5–88); p=n.s.].

The median symptom score decreased from 13 (IQR, 10–16) to 0 (IQR, 0–2) in group A and from 14 (IQR, 10–15.5) to 0 (IQR, 0–0) in group B, $p<0.05$.

A barium swallow was obtained in 40 of 51 patients (78.5%) after diverticulostomy and in 57 of 77 patients (74%) after open surgery. In all cases, a posterior pouch was still evident after diverticulostomy, though most of these patients were symptom-free. A small indentation was apparent in one

Table 3 Postoperative Complications

	Transoral approach (*n*=51)	Open surgery (*n*=77)	*p* value
Complication rate	3 (5.8%)	10 (13%)	n.s.
Cervical hematoma	–	4	
Transient left recurrent nerve palsy	–	1	
Left recurrent laryngeal nerve injury	–	1	
Mucosal perforation	1	1	
Pericarditis	–	1	
Tongue bleeding	1	–	
Leakage	–	2	
Mucosal tearing	1	–	

patient treated with myotomy alone, in another treated with myotomy plus diverticulectomy (both these patients were symptom-free), and in three who had also undergone diverticulopexy (and one of these had recurrent dysphagia).

Preoperative esophageal manometry was performed in 36 of 51 (70.6%) group A patients and 64 of 77 (83.1%) group B patients; it was repeated, a median of 8 months, after the operation in 19 of 36 (53%) of the former and 32 of 64 (50%) of the latter, showing significantly lower UES resting and intrabolus pressures in both groups (Figs. 1 and 2). The percentage of complete UES relaxations increased from 30% (IQR, 0–80) to 100% (IQR, 50–100; $p<0.005$) and from 20% (IQR, 0–80) to 80% (IQR, 57–100; $p<0.005$) in groups A and B, respectively. No differences were observed in pharyngeal/UES coordination before and after the treatment (pharyngeal/UES coordination was normal in most patients).

Analysis of Failures

On a single-patient basis, 11 patients (21.5%) in group A complained of persistent postoperative dysphagia, which required additional endoscopic procedures (to reduce the septum between the pouch and the esophagus) in eight cases. Three patients eventually required a surgical UES myotomy. On the other hand, only four patients (5.2%) in group B had recurrent dysphagia ($p<0.05$); they were treated with UES pneumatic dilations in three of four cases, while one refused any further treatment.

The demographics and clinical characteristics of patients in groups A and B with and without recurrent symptoms are presented in Table 4. Among those who had transoral diverticulostomy, three parameters were statistically influential in the patients who experienced a recurrence, i.e., age, size of diverticulum, and duration of symptoms. Nine of 11 symptomatic patients of group A had a diverticulum no more than 3 cm in length, giving a 36% chance of recurrence in the subgroup of patients with small diverticula treated transorally. (Table 5). These patients were also significantly younger and had lower overall symptom scores. In group B (open surgery), no parameters appeared

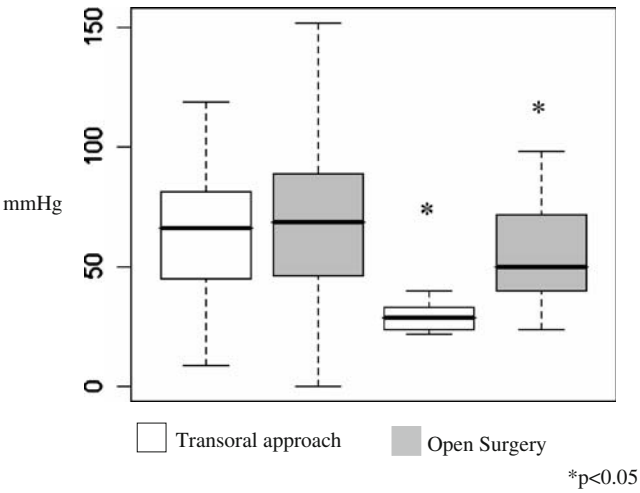

Figure 1 UES resting pressure decreased significantly in both groups. Group A: preoperative 67 mmHg (IQR 45–85) vs postoperative 29 mmHg (IQR 24–40); $p<0.05$. Group B: preoperative 69 mmHg (IQR 47.5–93) vs postoperative 50 mmHg (IQR 38.5–73); $p<0.05$. *Boxes* represent the interquartile range with the *horizontal line* representing the median value. *Error bars* represent maximum and minimum values.

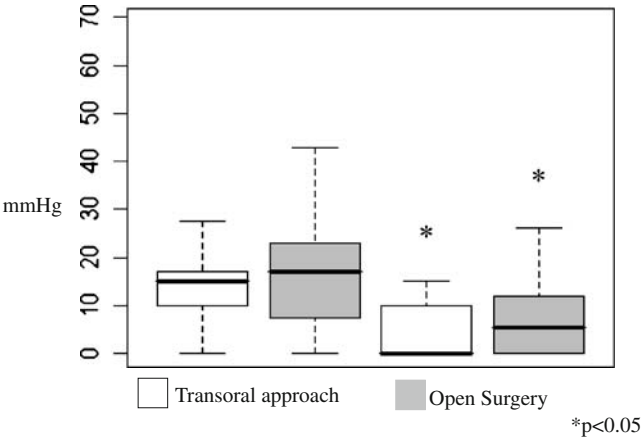

Figure 2 A significant drop in intrabolus pressure was recorded in both groups. Group A: preoperative 15 mmHg (IQR 10–18) vs postoperative 0 mmHg (IQR 0–10); $p<0.05$. Group B: preoperative 17 mmHg (IQR 6.25–23.5) vs postoperative 7 mmHg (IQR 0–12.25); $p<0.05$. *Boxes* represent the interquartile range with the *horizontal line* representing the median value. *Error bars* represent maximum and minimum values.

Table 4 Demographics and Clinical Characteristics of Patients With and Without Recurrences after Transoral ($n=51$) and Open Surgery ($n=77$)

	Good outcome	Failure	*p* value
Transoral surgery group			
n	40	11	
Age (years)	70 (62–77)	63 (54–71)	<0.05
Male/female	31/11	9/2	n.s.
Duration of symptoms (months)	18 (12–36)	18 (11–66)	n.s.
Symptom scores	13 (11–16)	11 (7–13)	<0.05
Size of pouch	3.5 (3–5)	3 (2–5)[a]	<0.05
Open surgery group			
N	73	4	
Age (years)	59 (35–66)	66 (59–72)	n.s.
Male/female	50/23	2/2	n.s.
Duration of symptoms (months)	18 (12–24)	24	n.s.
Symptom scores	14 (10–16)	12 (8.5–13.5)	n.s.
Size of pouch	2.5 (2–4)	1.25 (1–3.5)*	n.s.

Data are expressed as medians (IQR), as necessary
[a] Data are expressed as median and (range)

Table 5 Probability of being asymptomatic after treatment selected on the basis of pouch size

	Group A (n=51)		Group B (n=77)	
	≤3 cm	>3 cm	≤3 cm	>3 cm
Asymptomatic patients	16/25 (64%)*,**	24/26 (92%)*,**	50/53 (94.5%)**	23/24 (96%)**

*p<0.05 between the two subsets of patients (Fisher's exact test)
**p<0.05 for all series of patients (chi-square test)

to discriminate between patients whose treatment failed and those with a good outcome.

When preoperative manometric findings in patients with and without recurrence were compared, neither resting nor intrabolus UES pressures could discriminate between the two groups. Postoperative physiological findings in patients with and without recurrence are compared in Table 6: In both treatment groups, patients with recurrences had higher postoperative UES intrabolus pressures, that is to say, a smaller reduction in their UES intrabolus pressure, than patients whose surgery had been successful.

Final Results after Additional Treatments

Overall, after the primary treatment and any additional treatments for recurrent dysphagia, symptoms disappeared or improved significantly in 45 of 48 patients in group A (93.5%) and 70 of 73 in group B (96%).

Discussion

Though it was first described by Ludlow[14], the cricopharyngeal pouch is better known by the name of the German pathologist, Frederick Albert von Zenker, who published a review of 27 patients with this disease together with von Ziemssen. It is now accepted that Zenker's diverticulum is due to an outflow obstruction caused by a noncompliant fibrotic cricopharyngeal sphincter. Histological and functional studies on the muscle have revealed fibrosis, atrophy, hypertrophy, and inflammation.[15–17] Inadequate UES opening considerably increases hypopharyngeal intrabolus pressure and leads to the formation of a pulsion (Zenker's) diverticulum.[5,17,18]

For several decades, surgical therapy for cricopharyngeal diverticula focused on treating the sac by excision or pexis to the prevertebral fascia. But simple resection (or the pouch suspension) without a concomitant myotomy often caused severe complications, such as leakage from the suture line and failing to relieve dysphagia and being associated with a high rate of diverticulum recurrence. Cricopharyngeal myotomy directly addressed the pathogenesis of pulsion diverticula and soon came to be included as a fundamental part of the procedure. Thirty years later, an old endoscopic technique used to transect the septum between the diverticulum and the esophagus (initially with a cautery, but the rate of dehiscence was unacceptable)[6] remerged but using a laparoscopic stapler to simultaneously

Table 6 Postoperative Manometric Findings in Patients With and Without Recurrences

	Good outcome	Failure	p value
Transoral approach			
n	40	11	
UES resting pressure (mmHg)	9 (22–40)	33 (24–45)	n.s.
UES intrabolus pressure (mmHg)	8 (0–10)	12.5 (5–15)	<0.05
UES length (mm)	26 (22–32)	25 (19–30)	n.s.
Difference between pre- and postoperative UES resting pressure (mmHg)	45 (8–61.5)	49 (0–91)	n.s.
Difference between pre- and postoperative UES intrabolus pressure (mmHg)	−13 (−21/0)	0 (-10/3.5)	<0.05
Open surgery			
n	73	4	
UES resting pressure (mmHg)	43 (23.5–55)	50	n.s.
UES intrabolus pressure (mmHg)	5 (0–12)	16	<0.05
UES length (mm)	33 (29.5–33.5)	31	n.s.
Difference between pre- and postoperative UES resting pressure (mmHg)	−23 (−51.5/−13.5)	−17	n.s.
Difference between pre- and postoperative UES intrabolus pressure (mmHg)	−13 (−22/−5)	0	<0.05

Data are expressed as medians (IQR).
UES Upper esophageal sphincter, *n.s.* not significant

divide and suture the septum. Using this technique, the UES was divided too, thus obtaining physiological results similar to those of the open surgery, the only difference being that the pouch was not removed, a common cavity was created. This technique had its appeal because no incision was necessary, the procedure was quick to complete, risks related to transcervical approach were reduced, and patients recovered quickly, but it was not clear whether the results were fully comparable with those of open surgery and whether the method could be applied to all patients with ZD.

The results of this study confirm that both transoral and surgical procedures are safe and effective in treating Zenker's diverticulum. When stapling diverticulostomy is performed and the cricopharyngeal muscle fibers are divided, pharyngoesophageal manometry demonstrates a substantial reduction in subsequent UES resting pressures with both techniques, as reported by Ishioka et al.[19], too. The functional efficacy of the transoral approach in improving pharyngoesophageal function was also confirmed by the elimination of intrabolus pressure and the disappearance of any obstacle to bolus outflow (the advantage of endostapling over traditional surgery can be explained by the presence of a large common cavity, where small pressures are not easy to identify by perfusion manometry).

Our study confirmed the advantages of endostapling over conventional surgery, given the shorter operating time, little or no postoperative pain, quicker return to oral feeding, less severe complications, and shorter hospital stay.

The drawbacks of endoscopic diverticulostomy relate to certain patient features, e.g., the inability to open the mouth wide or to (over)extend the neck in cases of severe kyphosis and, more importantly, the size of the diverticulum. This study strongly suggests that if the diverticulum is ≤3 cm in size, recurrence may occur in 36% of patients. When a diverticulum is small, the anvil of the stapler is too long to be accommodated properly inside the pouch, so probably not all the UES fibers can be transected. Manometric studies in nine of 11 patients with severe dysphagia after their operation revealed incomplete UES relaxation and persistently high pharyngeal intrabolus pressure in four cases (44.5%): Three of these patients were reoperated and revealed uncut muscle fibers just below the end of the stapler line (and after myotomy they became asymptomatic). The strongest indication for endoscopic diverticulostomy is therefore a medium-sized diverticulum in which the stapler cartridge can be accommodated and the stapler can achieve an adequate cricopharyngeal myotomy, whereas diverticula shorter than 3 cm should be seen as a formal contraindication to the transoral approach.

The major drawbacks of open surgery are the related morbidity, mainly bleeding (a small drain is routinely left in place) and leakage from the suture line. Although our three leaks required no further surgery and healed spontaneously (after we had left the nasogastric tube in place, avoided oral feeding, and administered antibiotic therapy), it is nonetheless a severe potential complication in patients with concurrent respiratory or heart disease. Open surgery assures a complete and effective myotomy of the UES, especially in the subset of patients with small diverticula, for whom it should be considered the treatment of choice. After UES myotomy, small sacs (≤1.5cm) could be left in place, and they tend to disappear once the obstacle to outflow has been removed. Slightly larger diverticula (≤2 cm) can be introflected below the pharyngeal muscle layer to further reduce the risk of suture leakage. In our opinion, surgical myotomy is the therapy of choice for diverticula smaller than 3 cm.

In conclusion, this study on a larger number of patients confirms our previous observations: ZD can be treated effectively by endoscopic diverticulostomy or open surgery. Moreover, our analysis of treatment failures demonstrates that these are caused by a persistently noncompliant UES opposing the bolus outflow, as revealed indirectly by an unchanged pharyngeal intrabolus pressure. Based on these results, endoscopic diverticulostomy is better suited to medium-sized diverticula (3–5 cm). When applied to small diverticula, it carries a greater risk of failure in terms of persistent severe dysphagia because of an incomplete dissection of the UES. Open surgical myotomy, with or without diverticulectomy, is effective for diverticula of all sizes and should be considered the treatment of choice for small diverticula. It is important to bear in mind, however, that some of its complications, e.g. leakage or laryngeal nerve palsy, may have disastrous effects in elderly patients with comorbidities.

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Discussion

Tom R. DeMeester, M.D. (Los Angeles, CA, USA): Dr. Rizzetto, I congratulate you on a well constructed manuscript; I enjoyed reading it. Similarly, I enjoyed listening to your excellent presentation on this rather common problem of Zenker's diverticulum. The pathophysiology of the problem is largely understood at the present time. I appreciate the focus of your study on the therapeutic approach to the problem. Your study population was large, the follow-up long, and the extent of function studies obtained unique. I commend you on getting preoperative motility studies on these patients. It can be very difficult to get patient consent and to perform. You have nicely shown us and, I think for the first time, documented that a 3-cm diverticulum is not well managed with the endoscopic staple technique and leads to a high rate of recurrence.

I have four questions. First, you had two patients in whom you could not get the staple into the hypopharynx and into the diverticulum and had to convert to an open procedure. In the manuscript, you implied that some patients were difficult to do. Can you describe how hard you tried before you convert, and does the cervical spine or the ability of the patient to extend his head effect your decision to do the transoral procedure?

Second, is a motility study necessary in the common care of these patients at the present time?

Third, Dr. Jean-Marie Collard, who introduced the stapling technique, showed that there were some minor symptoms that persisted in the stapled group other than dysphagia and were due to the large common cavity created when you cut the septum between the diverticulum and the esophagus. Was your symptom evaluation careful enough to pick up those subtleties, or how do you explain the difference between his observation and yours?

Lastly, although this transoral approach suggests that it would protect the recurrent laryngeal nerves, we have seen some nerve palsy following the procedure. They were likely due to stretching of the nerve in trying to get the stapler in the hypopharynx. Would you comment on this and have you seen short-term palsies with this approach?

Christian, it was a superb presentation and, as a previous research fellow in our unit, you have given us reason to be very proud of you.

Christian Rizzetto, M.D. (Padova, Italy): Thank you very much for your kind words and comments. There are several issues to consider in deciding whether or not to perform the transoral procedure. The main appeal of this technique is that no incision is needed and the procedure is quick to complete. Zenker's diverticula frequently affect elderly patients, however, and the transoral procedure has its drawbacks in certain patients, e.g., if they are unable to open their mouth wide or to overextend their neck (in cases of severe kyphosis). In the two cases you mentioned, it was not easy to position the diverticular scope, and we had a mucosal perforation in one case. Basically, if we consider a patient a suitable candidate for the transoral approach, we normally try this procedure, but if we have trouble inserting the diverticular scope, then we usually opt to convert the procedure.

The second question addresses the manometry issue. I would say that this has been extremely important to our understanding of the pathophysiology of Zenker's diverticulum and is still important in the preoperative diagnostic work-up, especially in the case of small diverticula. Manometry can also play a part in patients experiencing recurrent dysphagia, to help us understand how it can be managed and the intra-bolus pressure adequately reduced.

Your third question refers to Collard's study. Our symptom questionnaire focused mainly on dysphagia and regurgitation, but other symptoms were assessed even though they did not count in the symptom score. We observed no differences, however, and the two patient groups were equally satisfied, in our experience at least. I think you have raised an intriguing point that warrants a prospective assessment.

Your last question was about laryngeal nerve palsy. We experienced transient palsy in one case and permanent recurrent laryngeal nerve injury in another: Both patients were in the open surgery group. It is hard to say how this might happen using the transoral approach, but—as you said—they were probably due to stretching of the nerve to accommodate the anvil of the stapler in the hypopharynx. I think exposure is the key issue in this type of surgery: The only way to avoid complications is to ensure adequate vision of the hypopharynx, the diverticulum, and the septum between the sac and the esophagus. In our opinion, the stapler should not be inserted and fired if the exposure conditions are less than optimal.

J Gastrointest Surg (2008) 12:2066–2077
DOI 10.1007/s11605-008-0712-7

Laparoscopic Repair of Giant Paraesophageal Hernia Results in Long-Term Patient Satisfaction and a Durable Repair

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Received: 30 May 2008 / Accepted: 18 September 2008 / Published online: 8 October 2008

Abstract
Background Laparoscopic repair of giant paraesophageal hernia (LRGPEH) is routinely performed in many centers, but high recurrence rates have led to concerns regarding this approach. We evaluate long-term recurrence rates, symptom improvement and correlation with radiographic recurrence, and risk factors for recurrence in our cohort of patients.
Methods A cohort of consecutive patients with a minimum of 5 years potential follow-up (1997–2003) post-LRGPEH was identified from a prospective database. Clinical outcomes, barium esophagram (BE), and quality-of-life (QoL) measures were obtained.
Results Laparoscopic repair was successful in 185/187 patients. Routine clinical follow-up (median 77 months) was available for all patients. Detailed questionnaires and BE were obtained in 65% and 82% of patients. Gastroesophageal Reflux Disease Health-Related QoL (GERD-HRQoL) scores were excellent to good in 86.7%. BE (median 51 months) demonstrated radiographic hernia recurrence in 15% of patients, but without consistent symptom association. There was a trend toward increased risk of radiographic recurrence in patients with a history of pulmonary disease ($p=0.08$). Seven reoperations (4.4%) were performed for symptomatic recurrence (median 44 months postoperative).
Conclusions LRGPEH performed in our minimally invasive center of excellence resulted in a durable repair with a high degree of satisfaction and preservation of GERD-related QoL at a median follow-up of over 6 years.

Keywords Laparoscopy · Hernia, hiatal · Outcome assessment (health care) · Recurrence · Gastroesophageal reflux

This work was presented at the Plenary Presentation of the 49th Annual Meeting of the Society for Surgery of the Alimentary Tract on May 21, 2008, at the San Diego Convention Center in San Diego, California.

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Introduction

In the early 1990s, the art of surgery underwent a dramatic shift with the widespread acceptance of minimally invasive techniques for upper abdominal surgery. Prior to this time, operations such as Nissen fundoplication, cholecystectomy, and transthoracic or transabdominal repair of giant hiatal hernia were often considered the last option for patients due to significant associated morbidity, pain, and prolonged recovery time. The advantages of laparoscopy, including reduced postoperative pain and rapid convalescence, were quickly realized, and many surgeons became interested in the application of laparoscopic techniques to the repair of giant paraesophageal hernia (GPEH). Although repair of GPEH is a very technically challenging operation which requires advanced laparoscopic skills, several reports were published in the mid-1990s establishing the feasibility and safety of the procedure.[1–6]

These early publications appeared to support the use of a laparoscopic approach to this disease process. A report by Hashemi and colleagues[7] from the University of Southern California in 2000, however, found a 42% incidence of radiographic recurrent hiatal hernia (median time of 17 months) in their series of 21 patients. Radiographic recurrence was not, however, associated with symptomatic complaints. This study was among the first to publish radiographic recurrence rates based on routine radiographic follow-up with video barium esophagram and raised concerns about the integrity and durability of the laparoscopic repair, despite the lack of association with symptoms. The high rate of radiographic recurrence from a center with extensive experience in esophageal surgery caused many surgeons to question the use of a laparoscopic approach to paraesophageal hernia.[8,9]

Since that time, many series have been published with short- to mid-term radiographic follow-up and report recurrence rates ranging from 1.9% to 33%.[8,10–18] Several of these studies were recently summarized in a meta-analysis, and the overall recurrence rate with objective radiographic follow-up was 25%.[19] When compared to the 1998 landmark paper by Maziak et al. reporting a 2% recurrence rate with long-term outcomes after open hiatal hernia repair,[20] these recurrence rates are unacceptably high.

The ongoing debate regarding outcomes after laparoscopic repair of giant paraesophageal hernia (LRGPEH) is fueled by a relative paucity of long-term radiographic and symptomatic assessment. The majority of studies have either reported on small numbers of patients, or short- to mid-term (less than 18–24 months) follow-up or both. These factors substantially limit the ability to draw conclusions about the long-term durability and effectiveness of this approach. In addition, the importance of radiographic recurrence is unclear, especially given the lack of correlation with symptoms. We sought to define the rates of long-term radiographic recurrence and reoperation, determine the correlation between symptomatic complaints and repair integrity following LRGPEH, and analyze the perioperative and patient factors which may contribute to the risk of recurrent symptomatic complaints and/or radiographic recurrences.

Methods

Operative Procedure Our operative approach to LRGPEH has been previously described.[14] Briefly, all patients underwent laparoscopic exploration, reduction of the hernia sac, extensive mediastinal mobilization of the esophagus, and sac resection. Seven surgeons performed these operations, although the majority (79.7%) were performed by the senior surgeon in the group (JDL). Length of the intra-abdominal esophagus was estimated with the esophagus resting in a neutral (no tension) position in the abdomen following sac reduction, circumferential esophageal mobilization including mediastinal dissection, division of the short gastric arteries, and mobilization of the anterior fat pad, taking care to preserve both the anterior and posterior vagus nerves. Complete dissection of the anterior fat pad away from the anterior esophagus exposes the gastroesophageal junction and allows for accurate assessment of the intra-abdominal esophageal length. A Collis esophageal lengthening procedure was performed when at least 2 cm of tension-free intra-abdominal esophagus was not achieved with this dissection. A fundoplication was routinely performed over a bougie (54–60 Fr). The crura were dissected, taking care to avoid disruption of the peritoneal lining and re-approximated without tension using heavy suture. If the crura were unable to be re-approximated without tension, or if the crura were attenuated or denuded of overlying peritoneum such that the ability to hold suture was compromised, mesh reinforcement with bioprosthetic mesh was performed. Large hiatal openings with intact peritoneal lining and well-developed mobile crura were closed primarily whenever possible, without routine mesh reinforcement.

Patient Cohort We performed an Institutional Review Board-approved retrospective review of prospectively gathered data in a surgical outcomes database. We were specifically interested in the long-term outcomes after LRGPEH. Therefore, the cohort of patients studied was defined as all patients with a potential 5-year follow-up (n= 187) who underwent LRGPEH at our center from January 1, 1997 to March 31, 2003. Routine postoperative clinical follow-up was complete in all patients. In order to obtain current long-term clinical follow-up information, attempts were made to contact each patient by telephone if they were not seen in the clinic. A minimum of four attempts were made to contact all patients. All patients were asked to obtain a current barium esophagram to evaluate for radiographic recurrence. Standard questionnaires to assess current symptoms were administered, including Gastroesophageal Reflux Disease Health-Related Quality of Life Questionnaire (GERD-HRQoL)[21] and Short-Form 36 Health Survey. All of the 187 patients had early clinical follow-up. During long-term follow-up (median 77 months), 34 patients (18%; 34/187) died, and we were unable to contact an additional 33 patients (18%; 33/187) for current follow-up information. Deaths were confirmed using the Social Security Death index or by family members. Perioperative deaths

occurred in two patients, both of whom were successfully discharged from the hospital but died within 30 days of surgery. One of the patients suffered a perioperative stroke during hospitalization and was discharged to a nursing facility. The other had an uncomplicated hospital course and was discharged to home. Additional details regarding their deaths were not available in the medical record. In the remaining 120 patients, current long-term clinical follow-up was obtained.

Database Data included preoperative patient characteristics, operative details, perioperative complications and follow-up information. All records regarding postoperative follow-up were obtained, including subsequent barium esophagram and need for re-operation for symptomatic recurrence. Results of current symptom assessment questionnaire, GERD-HRQoL instrument and the SF-36 Health Survey were recorded.

Since an esophageal lengthening procedure, by definition, leaves the patient with a gastroesophageal junction in an abnormal, potentially intrathoracic, position, only radiographic hiatal hernias with >10% or 2 cm of the stomach above the level of the diaphragm were considered significant recurrences. This is consistent with other publications, which define recurrence as more than 2 cm of the fundus above the hiatus.[22]

Statistical Analysis Statistical analysis was performed using STATA SE 8.0 Corp software.[23] The primary outcome variable was defined as radiographic recurrence. Secondary outcomes evaluated included need for reoperation for symptomatic recurrence, the GERD-HRQoL score,[21] SF-36 Health Survey, current symptomatic complaints, and use of proton pump inhibitors at the time of follow-up. Clinical symptoms on long-term follow-up were compared with the patient's preoperative complaints using McNemar's chi-square test for differences in proportions of paired outcomes. Fischer's exact test for differences between categorical variables was used where appropriate. Wilcoxon rank-sum test for differences between means was used to calculate the differences in SF-36 summary scores stratified by recurrent paraesophageal hernia. Univariate analyses were performed to calculate the risk of having the primary and secondary outcomes. Significance was determined at $p=0.10$ for inclusion in multivariate analysis. Because only history of pulmonary disease achieved this cutoff for p value, further multivariate analysis was not performed. To further investigate the trend toward significance in patients with a history of pulmonary disease, the analysis was repeated with stratification by preoperative pulmonary disease status.

Results

Laparoscopic repair of giant paraesophageal hernia was completed in 185 of 187 patients during this time period. Preoperative patient characteristics and technical aspects of LRGPEH were determined (Table 1). Conversion to an open repair was performed for adhesions ($n=1$) and inability to completely reduce hernia contents ($n=1$). All of the 187 patients had early routine clinical follow-up. Current follow-up information was obtained in 120

Table 1 Patient Characteristics and Technical Aspects of Laparoscopic Repair of Giant Paraesophageal Hernia (1997–2003)

	Number of patients (%)
Sex	
Male	55 (29)
Female	132 (71)
Age group (years by decade)	
Age <70	88 (47)
Age 70+	99 (53)
Charlson comorbidity score	
≥4	60 (34)
<3	114 (66)
Preoperative pulmonary disease	
Yes	35 (19)
No	146 (81)
Body mass index[a]	
Ideal	45 (27)
Overweight	55 (33)
Obese	44 (27)
Morbidly obese	22 (13)
History of ever smoking	
Yes	64 (36)
No	113 (64)
Preoperative hernia size[b]	
30% up to 50%	22 (14)
50% up to 75%	63 (39)
75% up to 99%	32 (20)
Complete intrathoracic stomach	43 (27)
Type of operation	
Fundoplication	183 (98)
Roux-en-Y	2 (1)
Gastropexy with gastrostomy tube	2 (1)
Esophageal lengthening procedure	
Yes	160 (86)
No	27 (14)
Crural reinforcement	
Yes	30 (16)
No	157 (84)

[a] BMI definitions: ideal = BMI <25, overweight = BMI 25 to <30, obese = BMI 30 to <35, morbidly obese = BMI ≥35

[b] By barium esophagram, preoperative endoscopy, or intraoperative findings

patients, including current symptom assessment, GERD-HRQoL surveys, and SF-36 Health Survey at a median time of 77 months (interquartile range (IQR) 62–92 months).

Recurrence of Paraesophageal Hernia

For the entire cohort of patients, at least one postoperative barium esophagram was obtained during clinical follow-up beyond 3 months in 154 (82%) patients; median time from operation to most recent barium esophagram was 50 months (IQR 3–77). For the 120 patients upon whom we were able to obtain current clinical follow-up, 102 had a barium esophagram available for evaluation at a median of 64 months after surgery (IQR 30–83). Barium esophagram revealed evidence for a radiographic recurrence in 23/154 patients (15%; Table 2). Of these, seven (4.4% of all repairs) have required reoperation at a median of 44 months postoperatively (range 8–81 months). A second recurrence after reoperation was identified in two patients, both of whom had large recurrent hernias with >50% of the stomach in the thorax.

Analysis of Factors Influencing Recurrence

In order to determine whether risk factors for recurrence could be identified in the dataset, selected patient characteristics, pertinent operative details, and radiographic findings were examined (Table 3). We tested for potential confounding variables (body mass index (BMI), sex, age-adjusted Charlson comorbidity index score ≥4, and use of esophageal lengthening procedure at the time of operative repair). There was no association between any of the independent variables and recurrent paraesophageal hernia on radiographic follow-up, although there was a trend toward increased incidence of recurrence in patients with preoperative pulmonary disease (odds ratio (OR) 2.6; 95% confidence interval (CI) 1.0, 7.0). Preoperative pulmonary disease was defined as any patient with a history of asthma, chronic obstructive pulmonary disease, emphysema, bronchiectasis, or interstitial fibrosis. Formal preoperative pulmonary function studies or other objective measures were only available for 12 of the 187 patients, precluding any additional analysis.

Table 2 Radiographic Findings on Long-Term Barium Esophagram: Number of Recurrences and Size of Recurrence

	Total (*n*, %)	Time from operation (median; IQR)
Postoperative barium esophagram	154 (82)	51 (3–77)
Total number of recurrences (>10% or 2 cm)	23 (15)	67 (36–81)
Size of recurrence as % stomach above diaphragm on barium esophagram[a]		
11–20	8 (5.6)	69 (23–78)
21–30	4 (2.5)	76 (58–92)
31–40	1 (<1)	67
41–50	1 (<1)	59
>50	2 (1.3)	60 (29–91)

[a] Size of the recurrence was not available for the seven patients who required reoperation for recurrence after their initial operation. The size of recurrence for the remaining 16 (of 23) recurrences are listed

Table 3 Risk of Radiographic Recurrence at Any Time After Operation by Preoperative Patient Characteristics and Operative Techniques

	Radiographic recurrence[c]		Crude OR (95% CI)
	Yes	No	
Sex			
Male	9	34	1.8 (0.7, 4.7)
Female	14	97	.
Age group (years by decade)			
Age 70+	11	69	0.82 (0.3, 2.0)
Age <70	12	62	.
Charlson comorbidity score			
≥4	9	41	1.4 (0.5, 3.5)
<3	13	82	.
Preoperative pulmonary disease			
Yes	8	22	2.6 (1.0, 7.0)
No	15	107	.
Body mass index[a]			
Ideal	4	32	.
Overweight	7	41	1.4 (0.4, 5.1)
Obese	5	33	1.2 (0.3, 5.0)
Morbidly obese	4	16	2.0 (0.4, 9.3)
History of ever smoking			
Yes	5	50	0.5 (0.2, 1.4)
No	16	77	
Preoperative hernia size[b]			
30% up to 50%	3	17	.
50% up to 75%	8	41	1.1 (0.3, 4.7)
75% up to 99%	1	29	0.2 (0.02, 2.0)
Complete intrathoracic stomach	5	32	0.9 (0.2, 4.2)
Type of operation			
Fundoplication			
Yes	21	129	0.2 (0.02, 1.3)
No	2	2	
Esophageal lengthening procedure			
Yes	19	115	0.7 (0.2, 2.2)
No	4	16	
Crural reinforcement			
Yes	5	21	1.5 (0.5, 4.4)
No	18	110	

[a] BMI definitions: ideal = BMI <25, overweight = BMI 25 to <30, obese = BMI 30 to <35, morbidly obese = BMI ≥35

[b] By barium esophagram, preoperative endoscopy, or intraoperative findings

[c] Includes only the patients with a follow-up esophagram evaluating for radiographic recurrence

Table 4 Paired Analysis of Relationship Between Preoperative Complaints and Current Symptoms

Symptom currently present?	Symptom present preoperatively?		p value[a]
	Yes	No	
Heartburn			
Yes	32	8	<0.0001
No	63	42	
Chest or epigastric pain			
Yes	1	8	<0.0001
No	71	55	
Dyspnea			
Yes	7	13	0.0003
No	39	78	
Dysphagia			
Yes	22	23	0.49
No	29	72	
Postprandial bloating			
Yes	11	21	0.39
No	28	75	
Regurgitation			
Yes	10	5	<0.0001
No	59	63	

[a] McNemar's chi-square for analysis of paired variables

In our results, esophageal lengthening procedure was performed in 86% (160/187) of patients. The majority of surgeons (six of seven) used esophageal lengthening when inadequate length of intra-abdominal esophagus was identified. We did not find a protective effect of esophageal lengthening procedure compared to those without (OR 0.7; 95% CI 0.2, 2.2). In addition, the use of crural reinforcement (16%; 30/187) was not associated with a reduced risk of radiographic recurrence in our series (OR 1.5; 95% CI 0.5, 4.4). Because of the small number of events, multivariate analysis was not performed and a type I error cannot be excluded.

Evaluation of Symptomatic Control

In order to determine whether LRGPEH resulted in long-term symptomatic control, patients were assessed for current symptoms including heartburn, chest pain, dyspnea, dysphagia, postprandial bloating, and regurgitation (Table 4). The presence of current symptoms was then compared to the preoperative complaints in paired analysis, and a statistically significant improvement in patient specific complaints of heartburn, chest pain, and dysphagia was identified at long-term follow-up. The proportion of patients complaining of current dysphagia or postprandial bloating was not significantly different than the proportion complaining of the same symptoms preoperatively (p=0.49 and p=0.39, respectively.) Current dysphagia was reported in 45 patients; 23 (51%) of these patients did not have preoperative symptoms of dysphagia recorded. Similarly, postprandial bloating is currently reported in 32 patients. Of these, 21 had complained of postprandial bloating prior to surgery, indicating this is a new complaint postoperatively in 11 (34%) of the 32 patients who now have postprandial bloating.

Analysis of Association Between Symptoms and Recurrence

We analyzed the risk of symptomatic complaint, stratified by radiographic recurrence. Chest pain and regurgitation were identified as the only significant associations between current symptomatic complaints and radiographic evidence for recurrent paraesophageal hernia on univariate analysis (Table 5). Patients with radiographic recurrence were 8.4 times more likely to complain of chest pain and 3.8 times

Table 5 Crude Odds of Recurrent Symptomatic Complaints, Stratified by Radiographic Recurrence of Paraesophageal Hernia and History of Preoperative Pulmonary Disease

Symptom currently present?[a]	Radiographic recurrence[b]			Preoperative pulmonary disease[c]		
	Yes	No	Crude OR (95% CI)	Yes	No	Crude OR (95% CI)
Heartburn						
Yes	6	29	1.2 (0.4, 3.5)	10	29	1.9 (0.8, 4.6)
No	13	75		16	87	
Chest pain						
Yes	5	4	8.4 (1.9, 38)	5	5	5.4 (1.4, 21)
No	15	94		19	103	
Dyspnea						
Yes	4	13	1.7 (0.5, 6.1)	7	12	3.1 (1.1, 9.2)
No	15	85		18	96	
Dysphagia						
Yes	9	32	1.9 (0.7, 5.1)	13	31	2.5 (1.1, 6.1)
No	11	75		14	85	
Postprandial bloating						
Yes	5	25	1.1 (0.3, 3.4)	7	25	1.4 (0.5, 3.7)
No	15	74		17	84	
Regurgitation						
Yes	5	8	3.8 (1.1, 13)	4	11	1.5 (0.4, 5.2)
No	15	90		23	96	
Current proton pump inhibitor						
Yes	8	44	1.2 (0.4, 3.2)	12	42	1.6 (0.7, 3.8)
No	11	71		15	86	

[a] Includes only those patients for whom the presence of the clinical symptom was evaluated (yes/no)
[b] Includes only the patients with a follow-up esophagram evaluating for radiographic recurrence
[c] Includes only patients with record of preoperative pulmonary status

more likely to complain of regurgitation. While the proportions of patients with dysphagia and postprandial bloating were not improved in current symptoms, there was no correlation with the findings of recurrent paraesophageal hernia. Because of the small number of recurrences and the rarity of each individual symptom, multivariate analysis was not performed. Current proton pump inhibitor use was identified in 35% of patients (56/159) but did not correlate with recurrent hiatal hernia in univariate analysis (OR 1.2, 95% CI 0.25–2.4).

Analysis of Quality of Life Indices

In addition to symptom assessment, validated quality of life measures were obtained to determine the impact of current symptoms on the patient's sense of well-being. GERD-HRQoL scores were obtained on 120 patients at a median of 77 months after repair (IQR 62–92 months; Table 6). A score of 0–5 was defined as excellent (94/120; 78%), 6–10 as good (ten of 120; 8%), 11–15 as fair (five of 120; 4%), and >15 as poor (11/120; 9%). Overall, 86% of patients had scores in the excellent or good category. When stratified by radiographic recurrence, 84% with recurrence were excellent or good compared to 85% excellent or good scores in patients without radiographic recurrence. Patients with radiographic recurrence did not have an increased risk of fair or poor results compared to those without evidence for radiographic recurrence (Table 6; OR 1.2; 95% CI 0.3, 4.8). Use of an esophageal lengthening procedure had no effect on GERD-HRQoL scores (data not shown).

Overall patient satisfaction was determined using the Short-Form 36 Health survey. The instrument measures eight domains of quality of life, including physical functioning, role physical, role emotional, bodily pain, vitality, mental health, social functioning, and general health. The responses were tabulated, and a physical component score (PCS) and a mental component score (MCS) were generated. In the general population, a score of 50 (standard deviation±10) represents the mean value. Results of the SF-36 were available for 109 patients (Table 7). Overall median PCS score was 52 (IQR 42–58) and median MCS score was 53 (IQR 50–56). Radiographic recurrence was associated with a higher PCS compared to those without radiographic recurrence (p=0.04), although the clinical significance of this finding is unclear. There was no difference between the two groups on the MCS score.

Because there was a trend toward increased risk of radiographic hiatal hernia recurrences in patients with preoperative pulmonary disease, patients were stratified by the presence or absence of preoperative pulmonary disease, and the risk of recurrent symptoms was determined. Patients with preoperative pulmonary disease were 5.4 times (OR 5.4; 95% CI 1.2, 21) more likely to complain of chest pain, 3.1 times more likely to complain of dyspnea (OR 3.1; 95% CI 1.1, 9.2), and 2.5 times more likely to complain of dysphagia (OR 2.5; 95% CI 1.2, 12) than were patients without pulmonary disease (Table 5). Patients with preoperative pulmonary disease were also 80% more likely to report fair-to-poor reflux-related quality-of-life scores, although this difference was not statistically significant (OR 1.8; 95% CI 0.5, 6.3). Finally, SF-36 Health Survey scores showed significantly reduce physical component summary scores in patients with preoperative pulmonary disease compared to those without preoperative pulmonary disease, reflecting the ongoing impact of dyspnea, chest discomfort, and dysphagia on physical and role physical function (Table 7).

The majority of patients were treated with fundoplication in this series (98%). There were, however, four patients who did not receive fundoplication (Table 1). Of these, two patients were treated with gastropexy and gastrostomy tube placement due to need for urgent intervention, advanced age in both patients (83 and 88 years), and severe associated comorbidities (age-adjusted Charlson comorbidity index score 7 and 5, respectively). One of these two patients recurred but was not reoperated. Both patients have

Table 6 Risk of a Fair or Poor Outcome on the GERD Health-Related Quality of Life Scores, Stratified by Radiographic Recurrence of Paraesophageal Hernia and History of Preoperative Pulmonary Disease

GERD-HRQoL Scale[a]	All patients	Radiographic recurrence[b]			Preoperative pulmonary disease[c]		
		Yes	No	Crude OR (95% CI)	Yes	No	Crude OR (95% CI)
	n=120	n=18	n=84		n=20	n=97	
Excellent or good	104 (86)	15	72	Ref.	16	85	Ref.
Fair or poor	16 (13)	3	12	1.2 (0.3, 4.8)	4	12	1.8 (0.5, 6.3)

[a] GERD-HRQoL scale: excellent (score 0–5), good (score 6–10), fair (score 11–15), poor (score >15)
[b] Includes only patients with barium esophagram and GERD-HRQoL score
[c] Includes only patients with record of preoperative pulmonary status and GERD HRQoL score

Table 7 Estimation of Patient Satisfaction Using the Short-Form 36 Heatlth Survey, Stratified by Radiographic Recurrence and History of Preoperative Pulmonary Disease

	All patients	Radiographic recurrence[a]			Preoperative pulmonary disease[c]		
		Yes	No	*p* value[b]	Yes	No	*p* value[b]
	n=109	*n*=15	*n*=83		*n*=17	*n*=90	
Physical component summary	52 (42-58)	58 (50-58)	52 (41-48)	0.04	46 (34-51)	54 (45-58)	0.003
Mental component summary	53 (50-56)	53 (48-55)	53 (50-56)	0.76	53 (46-58)	54 (51-56)	0.52

[a] Includes only patients with barium esophagram and SF-36 score
[b] Wilcoxon rank-sum test for differences between means
[c] Includes only patients with record of preoperative pulmonary status and SF-36 score

died during follow-up. The remaining two patients were treated with Roux-en-Y gastric bypass for BMI of 40. One patient has a radiographic recurrence but has not required a reoperation. Both patients are still alive, with GERD-HRQoL scores of "Excellent" for the patient without recurrence and "Good" for the patient with documented radiographic recurrence at most recent follow-up.

Discussion

Based on the current literature, outcomes after laparoscopic repair of giant paraesophageal hernia are variable, and long-term follow-up is limited in most studies. This study is the largest cohort of patients reported to date with long-term radiographic follow-up after LRGPEH. We found low rates of reoperation and radiographic recurrence. Overall, patients were satisfied with surgery, with good to excellent scores on validated reflux-related quality of life measures. While mild symptomatic complaints are frequent, the only symptoms which correlate with findings of recurrent hiatal hernia on radiographic evaluation are chest discomfort and regurgitation in univariate analysis. This suggests that other patient-related factors are also important in determining long-term symptom relief. Current complaints of dysphagia and bloating may be related to the operative repair, technical failures such as wrap disruption, tight wrap, or improper wrap placement on the proximal stomach, or patient characteristics such as esophageal motility disorders or pulmonary disease more that to findings of radiographic recurrence. We also analyzed for potential preoperative factors which may contribute to the risk of long-term radiographic recurrence. We found that a history of pulmonary disease at the time of repair may identify patients who are at increased risk of radiographic recurrence as well as persistent or recurrent symptomatic complaints, independent from recurrence of the hernia.

Short- and mid-term recurrence rates as high as 42% have been reported with the laparoscopic approach to repair of giant paraesophageal hernia, with an overall radiographic recurrence of 25%.[1,7,8,10,11,13–16,19,24–27] Significant debate has ensued regarding factors impacting on risk of recurrence. Variables such as the need for esophageal lengthening procedures,[16,28–30] reinforcement of the hiatal closure,[4,12,22,31–33] and use of fundoplication[34] have undergone much scrutiny. Our approach to LRGPEH during this time period has been previously described[14,26] and is based on the principles of open repair, including reduction of the hernia contents, complete sac removal from the mediastinum, extensive esophageal mobilization, and accurate identification of the gastroesophageal junction for determination of esophageal length by mobilization of the anterior gastroesophageal fat pad. It is critically important to ensure a tension-free and adequate length of intra-abdominal esophagus to prevent excessive pressure loading of the hiatal repair. Liberal use of esophageal lengthening procedure (86%) in our series may be one of the reasons for the low rate of recurrence observed in comparison to others although our data did not show a statistically significant reduced risk compared to those repaired without esophageal lengthening. Crural reinforcement is used very sparingly at our center, but without hesitation if there are problems with crural integrity or tension.

Radiographic recurrence rates from the open surgical literature varied widely over the years, from as high as greater than 20% to the best reported rates of 2%.[7,20] This is similar to the ranges reported for the laparoscopic approach and may be considered comparable. However, even in the hands of very experienced minimally invasive esophageal surgeons, a radiographic recurrence rate of 15% and 4% rate of reoperation remains higher than the 2% recurrence and reoperation rate reported in the best open experience.[20]

An important goal of our surgical outcomes database is to identify preoperative or perioperative characteristics which may help to identify patients who are at risk for long-term adverse outcomes, including symptomatic complaints and hernia recurrence. With the exception of a trend towards increased risk of recurrence and symptomatic

complaints in patients with preoperative pulmonary disease, this study did not identify any preoperative patient characteristics or perioperative factors that were significantly associated with risk of recurrence. This is in contrast to the reported literature and warrants further discussion. Esophageal lengthening (Collis gastroplasty) and crural reinforcement, in particular, are technical aspects of repair which have strong proponents and detractors. Others, including a meta-analysis of the available laparoscopic literature,[19,35] have reported that esophageal lengthening procedures may protect against recurrent hernia by unloading the tension on the crural repair. We did not demonstrate a significant protective benefit in our cohort of patients. It is possible that the extremely high prevalence of esophageal lengthening procedures used (86%) may be contributing to a type I error. In other words, liberal use of esophageal lengthening to ensure an adequate length of intra-abdominal esophagus may be the reason that we have a low rate of long-term recurrence compared to the higher rates of short- and mid-term recurrence reported by others, but the numbers of patients without an esophageal lengthening procedure and the recurrences within this small group of patients (n=27) are too low to reveal this finding.

We also failed to demonstrate a protective benefit of crural reinforcement, which others have also shown to be beneficial. This question has been formally tested in a randomized trial[22] as well as a recent meta-analysis.[36] Both suggest a significant reduction in the risk of recurrence in patients with mesh reinforcement compared to those without reinforcement, but equipoise remains within the surgical community about the indications for mesh reinforcement. Mesh reinforcement was rarely used in our cohort (16%), and, given the low number of recurrences, a lack of protection against recurrence may be the result of a type I error. It is possible that the protective benefit of mesh was not realized because mesh was only used in those patients for whom a crural repair could not be performed without tension or with highly attenuated crura. In this report, our radiographic recurrence rate was 15% at 50 months median follow-up. While a randomized trial has demonstrated a significant reduction in the risk of early recurrence with mesh, from 24% to 9%, this trial rarely used esophageal lengthening and follow-up was only available up to 6 months. It is difficult to directly compare this study with our results, particularly given the difference in length of follow-up. It is likely, however, that the ideal repair occurs when the surgeon possesses the technical skills necessary to use mesh reinforcement and/or esophageal lengthening when appropriate, based on the patient's anatomy.

Since this study includes retrospective collection of the preoperative and perioperative data, our findings must be considered hypothesis generating rather than providing conclusive results. For example, we found that long-term symptomatic complaints including dysphagia and chest discomfort were associated with preoperative pulmonary disease. These patients showed a trend toward an increased risk of radiographic recurrence; this is not surprising given the chronic cough, hypoxia, and use of accessory respiratory muscles with resultant increases in intra-abdominal pressures found in this population. A patient with a history of preoperative pulmonary disease and a recurrent hernia was 2.5 times more likely to complain of dysphagia and 5.4 times more likely to complain of chest pain. Future studies addressing this question would include preoperative and postoperative comprehensive pulmonary function data, esophageal emptying, and motility studies and gastric functional studies.

This study has several strengths and limitations. Because the current radiographic and clinical data is cross-sectional rather than time series in nature, the ability to accurately define the time course of radiographic and symptom recurrence is obviously limited. However, the use of standardized validated symptom scores provides clinical measures which can be followed and replicated over time. These symptom outcomes measures and barium esophagram are now routinely obtained in our center, regardless of symptoms, as part of our clinical pathway to monitor for recurrence. This minimizes, but does not eliminate, the impact of referral bias on the rate of radiographic recurrence reported in this study. An additional strength derives from the large number of patients with long-term clinical and radiographic follow-up. This allows for in-depth analysis of variables which may be associated with risk of recurrence and symptomatic complaints.

Another potential limitation derives from the use of percentage of intrathoracic stomach as a marker for hiatal hernia size. While giant paraesophageal hernia has been previously described by us and others[13,17,26] as the presence of at least 30% of the stomach above the diaphragm on preoperative video esophagram, this measure as a surrogate for hiatal opening is crude compared to intraoperative measures, such as hiatal surface area or diameter in centimeters. Due to the retrospective nature of this database and the lack of standardized objective intraoperative measures, percent intrathoracic stomach, estimated on preoperative barium swallow, is the most objective measure obtainable, followed by computed tomography scans of the abdomen and surgeon's intraoperative estimate. An objective measure of hiatal opening, such as the hiatal surface area described by Granderath and colleagues,[37,38] may provide more precise data about which patients are at risk for radiographic recurrence and who may benefit from mesh reinforcement. Clearly, further work utilizing large volume, in-depth, prospective preoperative, and perioperative data analysis is necessary to further define these and other risk factors for recurrence.

Conclusions

Our data demonstrate that the efficacy and long-term durability of a laparoscopic approach to repair of giant paraesophageal hernia was comparable to open surgical series in our esophageal institute with extensive minimally invasive and open experience. Radiographic recurrence rates are low. Reoperations for recurrence are low (4%) and comparable to the best open series. Patients report significant symptomatic improvement in complaints of heartburn, chest or epigastric pain, dyspnea, and regurgitation compared to their preoperative symptoms. In our center, which specializes in minimally invasive esophageal surgery, a laparoscopic approach to the repair of GPEH resulted in excellent long-term clinical and radiographic outcomes, comparable to the best open series.

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Discussion

Laparoscopic Repair of Giant Paraesophageal Hernia Results in Long-Term Patient Satisfaction and a Durable Repair

Carlos A. Pellegrini, M.D., (Seattle, WA): I think this paper, with its abundant data and long follow-up, provides a benchmark against which to compare anyone's results. As it becomes widely quoted and a true landmark, I am afraid it may also lead to an unintended consequence and that is, that the average physician will take the conclusions to mean that this is a safe operation, this is an operation that I can do, and this operation leads to a recurrence rate of 15% with a need for reoperation of only 4%. I think these results are achieved by your group in part as a reflection of the large volume of patients you do that in itself a reflection of the dedicated way esophageal surgery is handled in your center. With that in mind, perhaps the most important thing you may want to consider is to provide the ingredients that you think are needed to achieve these results. What is it that you do that you think impacts most in your results? How can you have such a low rate of recurrence and in particular or reoperations?

On the other hand, 15% is still higher than the 8% that we found with Drs. Hunter, Jobe, and others in the prospective randomized multicenter trial that we reported with the use of mesh, and we had it at 24% when we did not use mesh. So my next question is, why not use mesh more frequently since you still have a 15% recurrence rate.

The last two questions that I have are related to the symptoms, and I am surprised that, in the paper, at least, you make very clear emphasis that the presence of a radiographic recurrence did not seem to make any difference in the symptoms. So, patients got better whether they recurred or they did not recur. I think that that is probably right, because the recurrences were relatively small, and, therefore, it is not the same thing as having that floppy sac in the mediastinum. But it makes me question why did you reoperate on some of those patients? Were those the larger hernias? Or what is your indication (a) for operation and (b) for reoperation? The second question stems from the observation that you made on the issue of aspiration. Patients with pulmonary disease or bronchiectasis are the ones that probably are aspirating and need this repair the most. So, since they tend to do the worse, what is your advice for those patients? In our study, we found that chest pain, early satiety, and physical function on the SF-36 were three clear characteristics of those who recurred, but you did not find that.

Katie S. Nason, M.D. (Pittsburgh, PA): Thank you, Dr. Pellegrini. I will try to get through these in the order that they were asked.

First, to elaborate on the procedure that we perform, we do an extensive mobilization of the esophagus circumferentially all the way to the level of the carina, beginning first with the reduction of the sac. We actually go into the mediastinum, grasp the sac, and completely ignore the stomach that is within the mediastinum. Doing that allows us to bring the stomach back into the abdomen with the sac rather than trying to pull the stomach back down into the abdomen. This minimizes trauma to the stomach. After you are done dissecting the mediastinum, when you pull back and look with the camera, you see a stomach lying nicely within the abdomen and no portion back up into the mediastinum. If we do not see that, we know that our mediastinal dissection is not complete.

Having circumferentially mobilized the esophagus to the level of the carina or higher if possible, we then evaluate the location of the GE junction. In order to do this, we actually mobilize both the anterior and the posterior fat pad and clearly visualize the gastroesophageal junction both endoscopically and laparoscopically to determine the length of esophagus that is within the abdomen. We try to keep our insufflation pressures as low as possible, usually in the range of 10 to 12 mm of pressure, in order to minimize the

cephalad distraction of the diaphragm and truly determine what the length of intra-abdominal esophagus is.

After assessing esophageal length, we then decide whether or not to proceed with the Collis lengthening procedure in order to ensure that we have at least 3 to 4 cm of intra-abdominal esophagus upon which to perform our wrap.

Your second question had to do with symptoms and the indication for operation. In a subset of our patients, the indication for operation was anemia. They did not have any symptomatic complaints that you could relate to a paraesophageal hernia. Another subset of our patients actually had what you describe as significant pulmonary dysfunction related to aspiration, and several patients had multiple hospitalizations for recurrent pneumonia, many patients had adult-onset asthma and that was often an indication for repair in our population. The final indication are the classic complaints of gastroesophageal reflux, chest pain, regurgitation/vomiting, and dysphagia.

Finally, the indications for reoperation really have to do with symptoms, including recurrent anemia as well as symptomatic complaints. The seven patients that had reoperation, six of them were reoperated in our center, and all of them had recurrent significant complaints that were relieved by reoperation. The two patients with the large recurrences who do not want reoperation are currently only minimally to asymptomatic and really do not want to go through another operation because it just does not really impact on their quality of life.

Finally, to address the use of mesh, the follow-up in the paper you describe with the randomized trial, you see mesh versus no mesh with an 8% recurrence rate at 6 months. The recurrence rate on our radiographic follow-up is 51 months in this setting. So, it is hard to know how to compare those two papers one to the other.

We do a very extensive mobilization. Bringing the sac down into the abdomen and fully mobilizing the stomach off the crura is an important part of the operation, and taking the phrenoesophageal ligaments all the way down and completely freeing up the crura has allowed us to re-approximate many of these crura without tension and without the need for mesh reinforcement. However, with a recurrence rate of 15%, there is obviously more to do to reduce the rate of recurrence over time. More liberal use of mesh, particularly in patients with pulmonary dysfunction, may be an interesting way of reducing the risk of recurrence over time. At least in our paper, those patients are at higher risk of recurrence, and it may be that we can study that more completely to make a better determination in the future.

David W. Rattner, M.D. (Boston, MA): One question and one comment. My first question is, if I read the slide correctly, it looked like 85% of patients had esophageal lengthening procedures, which is really very high compared to my practice and many others. I wonder if you think that contributed to the high rate of postoperative heartburn, because if I read that slide correctly, about 40% of your patients had heartburn postoperatively.

My other comment is that you used a paper that we wrote sort of as a straw man for your argument, and I just want to clarify that the message in that paper was the mere presence of a paraesophageal hernia is not an indication for surgery, at least not in our hands, and I do not think you can make any conclusion based on a retrospective data set of your own personal series as to whether or not asymptomatic patients should be operated on or not. So I think you need to temper your conclusions a little bit, unless you have data that you have not shown us.

Dr. Nason: You are absolutely correct as far as not offering patients who are asymptomatic an operation that has the possibility of making them symptomatic, and certainly doing any kind of antireflux procedure can often lead to symptoms that the patient does not really want, such as excessive flatulence and dumping syndrome. We have found, however, that if you carefully talk to these patients that very few of them are truly asymptomatic. If you present them with a symptom assessment that is standardized, very often you will be able to dissect out problems that they are having and changes in their lifestyle that they have made in order to accommodate for the finding of paraesophageal hernia. Certainly, there are patients who are not currently being referred for surgery being treated with serial dilations for dysphagia who may benefit from the operation.

I think we have to be careful in both directions of saying that once we have carefully assessed for symptoms, if the patient is truly asymptomatic, then operating on them is probably not going to be in their favor, but it requires a careful symptom assessment, looking for symptoms of anemia, looking for symptoms of pulmonary dysfunction, and looking for atypical symptoms of reflux before you say that they are truly not symptomatic.

Steven R. DeMeester, M.D. (Los Angeles, CA): Congratulations, great series. You have had the opportunity to see 5- and, some probably, 10-year barium studies in these patients because of the length of the series. Are you able to provide any indication of the timing of recurrence? Did any of the patients have earlier barium studies where you can tell us whether the risk of recurrence levels off at some point and we do not need to worry about it?

Dr. Nason: We unfortunately do not have time series analysis on these patients and that is actually one thing that we have addressed in the last year and a half or so, and we have actually instituted a clinical pathway where patients

come back every one to 2 years to get a surveillance barium esophagram, because we found that the patients that we sent out, many of them actually had symptomatic complaints that we could help them with, particularly symptoms of dysphagia that would respond to dilatation, not in the setting of a recurrent hernia but just a slightly tight wrap or some other process that is causing them to have dysphasia. Following those patients over time actually allows us to intervene and maintain some degree of a better quality of life than if they were just left on their own. So, we hope to have some data to report on that in the not too distant future.

J Gastrointest Surg (2008) 12:2078–2086
DOI 10.1007/s11605-008-0705-6

Acinar Cell Carcinoma of the Pancreas in the United States: Prognostic Factors and Comparison to Ductal Adenocarcinoma

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Received: 19 May 2008 / Accepted: 8 September 2008 / Published online: 3 October 2008

Abstract
Introduction Pancreatic acinar cell carcinoma (ACC) is a rare tumor with poorly defined prognosis.
Objective Our objective was to compare a large population of patients with ACC to pancreatic ductal cell adenocarcinoma (DCC) in order to determine distinguishing characteristics and to assess survival.
Methods Patients were identified from the National Cancer Database. Regression methods were used to identify differences between ACC and DCC and to identify predictors of survival for resected ACC. Eight hundred sixty-five patients with ACC were identified.
Results Median tumor size was 6.9 cm (vs. 4.6 cm DCC); 32.1% had nodal metastases (vs. 48.0% DCC); and 47% had high-grade tumors (vs. 37.3% DCC). Resection margins were R0 77.3%, R1 13.7%, and R2 9.0%. Patients with ACC were more likely to be male, white, and have larger tumor size, no nodal involvement, or pancreatic tail tumors. Stage-specific 5-year survival was significantly better for resected ACC vs. DCC Stage I: 52.4% vs. 28.4%, II: 40.2% vs. 9.8%, III: 22.8% vs. 6.8%, and IV: 17.2% vs. 2.8%. On multivariable analysis, age < 65, well-differentiated tumors, and negative resection margins were independent prognostic factors for ACC.
Discussion ACC carries a better prognosis than DCC. Aggressive surgical resection with negative margins is associated with long-term survival in these more favorable pancreatic cancers.

This paper was presented at the Society for Surgery of the Alimentary Tract (SSAT) in San Diego, CA, USA, in May 2008.

Grant Support: KYB is supported by the American College of Surgeons, Clinical Scholars in Residence program.

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Keywords Pancreatic adenocarcinoma · Acinar cell carcinoma · Surgery · Pancreatectomy · National Cancer Data Base · Resection

Introduction

Pancreatic acinar cell carcinoma (ACC) is a rare tumor with a poorly defined natural history. The prognosis of patients with ACC as well as outcomes following resection is also not well understood. The experience to date with ACC has largely been characterized by small single institution series.[1–7] More recently, multi-institutional series and the Pancreatic Cancer Registry of the Japan Pancreas Society (n=115) have also been examined.[8,9] Still, the number of patients examined is small; thus, conclusions are limited.

In this study, using the National Cancer Database (NCDB), we examined a large population of ACC (n=

865) and compared it to the more common tumor, pancreatic ductal cell adenocarcinoma (DCC). In so doing, we sought to determine unique aspects of ACC compared with DCC. We also wanted to assess whether there was a difference in survival of ACC compared to DCC.

Methods

Data Acquisition and Patient Selection

The NCDB is supported by the American College of Surgeons, the Commission on Cancer, and the American Cancer Society.[10,11] The NCDB now contains data on over 21 million cancer patients diagnosed from 1985 to 2005. Based on incidence estimates from the American Cancer Society, the NCDB captures approximately 74% of newly diagnosed pancreatic cancers in the United States each year.[11] The NCDB collects information regarding patient demographics, diagnosis, tumor characteristics, staging, treatment, and survival.

Using the NCDB, patients diagnosed with pancreatic malignancies from 1985 to 2005 were identified based on *International Classification of Diseases for Oncology* (second and third editions) site and histology codes.[12] At the time of this study, 2005 diagnoses were the most recent cases available for analysis. Patients were dichotomized into those with ductal adenocarcinoma and those with acinar cell carcinoma (ICD-O code 8550). Patients with neuroendocrine tumors were excluded. Patients who underwent pancreatectomy were identified based on the CoC's *Registry Operations and Data Standards* and the *Facility Oncology Registry Data Standards* site-specific procedure coding.[13,14] Pancreatectomy is defined as pancreaticoduodenectomy (with or without pylorus preservation), partial or distal pancreatectomy, total pancreatectomy, and pancreatectomy not otherwise specified (NOS). All patients were restaged according to the American Joint Committee on Cancer (AJCC) sixth Edition *Cancer Staging Manual*.[15,16] As a large proportion of patients did not undergo surgery, clinical TNM and/or AJCC overall stage were combined with pathologic staging to ascertain the most accurate overall stage. Patients were excluded if they had in situ disease or were less than 18 years of age at the time of diagnosis.

Statistical Analysis

Descriptive statistics were calculated for all variables. Categorical variables were compared using the chi-squared test. Medians were compared using the Mann Whitney *U* test. Trends over time were compared using the chi-squared test for trend.

Forward stepwise multiple logistic regression was used to examine differences between ACC and DCC. All patients (surgical and nonsurgical) were included in the analysis. Factors assessed in the model included gender, age (<55, 56–65, 66–75, 76–85, >85 years), race or ethnicity (white, black, Asian, Hispanic, other), size (<2.0, 2.1–4.0, >4.0 cm, and T classification), nodal status, distant metastases, and tumor location within the pancreas (head, body, tail, and diffuse or NOS). Odds ratios with 95% confidence intervals were generated. The Hosmer–Lemeshow goodness-of-fit test and the c statistic of the receiver operator characteristic curve were used to assess the model.[17]

Survival was calculated in months as the time from the index operation to death or last contact. Survival was estimated by the Kaplan–Meier method and compared using the log-rank test.[18] Cox proportional hazards modeling was used to assess the association of patient, tumor, treatment, and hospital factors on survival at 5 years after resection for ACC.[19] Factors examined in the Cox model included gender, age (<55, 56–65, 66–75, 76–85, >85 years), race or ethnicity (white, black, Asian, Hispanic, other), T classification, nodal status, distant metastases, tumor grade (well- or moderately differentiated vs. poorly differentiated), margin status (R0 vs. R1/R2), treatment modality (surgery only vs. surgery with adjuvant therapy), hospital type (National Cancer Institute-designated cancer centers, other academic hospitals, Veterans Administration facilities, and community hospitals), and the year of diagnosis (1985–1990, 1991–1995, 1996–2000). An indicator variable was used when tumor grade data were not available due to the large number of patients with missing data on the degree of tumor differentiation. The proportional hazard assumptions were confirmed graphically. Hazard ratios with 95% confidence intervals were generated.

The level of statistical significance was set to $P < 0.05$. All P values reported are two-tailed. Statistical analyses were performed using SPSS, version 15 (SPSS Inc., Chicago, IL, USA). This study protocol was reviewed by the Indiana University and Northwestern University Institutional Review Boards.

Results

From 1985 to 2005, 865 patients with ACC and 367,999 patients with DCC were identified. ACC accounted for 0.2% of all pancreatic cancers reported to the NCDB and approximately 0.5% of resected pancreatic cancers, and these proportions remained unchanged from 1985 to 2005 ($P = 0.91$, $P = 0.47$). The 865 cases of ACC were reported

by 529 hospitals with no institution reporting more than 16 cases.

Comparison of ACC and DCC

Compared to patients with DCC, those with ACC were younger (median 67 vs. 70 years) and more frequently male (63.5% vs. 49.9%; Table 1). Patients with ACC had larger tumors (4.0 vs. 5.9 cm) but more frequently presented at an earlier Stage (Stage I/II 34.6% vs. 22.4%) and without distant metastases (66.5% vs. 61.0%). ACC was more frequently located in the tail of the pancreas compared to DCC. On multivariable analysis, patients with ACC were more likely to be male, white, have larger tumors, or lesions in the body or tail of the pancreas (vs. head; Table 2).

Of the 865 patients with ACC, 333 (38.5%) underwent resection; whereas, 62,167 of 367,999 (16.9%) patients with DCC underwent resection (Table 3). For ACC, 44.1% underwent a pancreaticoduodenectomy, 22.2% underwent a distal pancreatectomy, 9.9% underwent a total pancreatectomy, and the procedure was not specified in 26.8%. Adjuvant therapy was utilized for ACC in 42.9% patients, while surgery was the only treatment for 57.1% of patients.

Median follow up was 22.2 months in the ACC group and 11.2 months in the DCC group. For ACC, 5-year survival in resected patients was significantly better than in patients who did not undergo resection: 36.2% (median 27 months) vs. 10.4% (median 7.1 months), $P<0.0001$. Stage-specific survival was significantly better for resected ACC compared to DCC (Fig. 1): Stage I: 52.9% vs. 30.9% ($P=0.001$), Stage II: 39.9% vs. 10.6% ($P<0.0001$), and Stage III: 20.4% vs. 6.7% ($P=0.006$). Median survival of ACC compared to DCC according to stage was stage I: median not reached vs. 24.3 months, stage II: 26 vs. 13.9 months, stage III: 22.6 vs. 10.3 months.

Prognostic Factors

On univariate analysis of resected patients, younger age, earlier T classification, well-differentiated tumors, R0 status, and earlier stage were associated with better long-term survival (Fig. 2). Five-year survival according to T

Table 1 Patient Characteristics

		Acinar cell carcinoma	Ductal cell carcinoma	Significance
Number of patients		865	367,999	
Gender				$P<0.0001$
	Male	63.5%	49.9%	
	Female	36.5%	50.1%	
Median age (IQR) years		67 (55–75)	70 (61–78)	$P<0.0001$
Race/ethnicity				$P=0.012$
	White	83.4%	81.3%	
	Black	7.9%	11.1%	
	Asian	1.8%	1.8%	
	Hispanic	5.3%	4.0%	
	Other	1.6%	1.8%	
Median tumor size (IQR) cm		5.9 (4.0 - 8.0)	4.0 (3.0 - 5.1)	$P<0.0001$
Stage				$P<0.0001$
	I	14.1%	6.7%	
	II	20.5%	15.7%	
	III	11.6%	8.8%	
	IV	33.5%	39.0%	
	Unknown	20.2%	29.8%	
Location within pancreas				$P<0.0001$
	Head	42.3%	55.1%	
	Body	7.6%	8.8%	
	Tail	19.8%	9.4%	
	Other	30.3%	26.8%	
Hospital type				$P=0.30$
	NCI Cancer Center	11.1%	10.0%	
	Other academic	31.2%	29.0%	
	VA	1.5%	1.9%	
	Community	56.2%	59.1%	

IQR interquartile range, *NCI* National Cancer Institute, *VA* Veterans' Administration

Table 2 Factors Associated with Acinar Cell Carcinoma Compared to Ductal Cell Adenocarcinoma

	Odds ratio (95% confidence interval)	Significance
Gender		
Female	1.0 (Referent)	
Male	1.75 (1.36–2.26)	$P<0.0001$
Race/ethnicity		
Black	1.0 (Referent)	
White	2.07 (1.20–3.59)	$P=0.009$
Asian	1.21 (0.39–3.74)	$P=0.74$
Hispanic	1.18 (0.47–2.95)	$P=0.73$
Other	1.12 (0.32–3.96)	$P=0.86$
Tumor size		
<2.0 cm	1.0 (Referent)	
2.1–4.0 cm	1.36 (0.83–2.21)	$P=0.22$
>4.0 cm	3.70 (2.35–5.83)	$P<0.0001$
Nodal metastases		
Present	1.0 (Referent)	
Absent	1.80 (1.36–2.38)	$P<0.0001$
Location within pancreas		
Head	1.0 (Referent)	
Body	1.98 (1.22–3.20)	$P=0.006$
Tail	3.60 (2.64–4.93)	$P<0.0001$
Other/diffuse/NOS	2.09 (1.48–2.96)	$P<0.0001$

Odds ratios >1.0 indicate a higher likelihood of acinar cell carcinoma compared to ductal cell carcinoma. Factors that were not significant in the model were age, distant metastases, and tumor grade. Comparison includes all patients (surgical and nonsurgical)
NOS not otherwise specified

classification was T1: 52.4%, T2: 40.2%, T3: 22.8%, and T4: 17.2% (Fig. 2A). Node status was not associated with long-term survival (Fig. 2B). Five-year survival in node negative compared to node positive patients was 41.2% vs. 32.0% with a median survival of 29.4 vs. 26 months, respectively. Low-grade ACC had a 54.8% 5-year survival rate (median survival not reached), while high-grade ACC had a 27.1% 5-year survival rate (median survival 19.4 months; Fig. 2C). Five-year survival according to R status was R0: 38% (median survival 34.4 months), R1: 21.5% (median survival 12.4 months), and R2: 16.7% (median survival 16.1 months; Fig. 2D). Overall stage-specific survival was stage I 52.9% (median survival not reached), stage II 39.9% (median survival 26 months), and stage III 20.6% (median survival 22.6 months; Fig. 2E).

Adjuvant chemotherapy was associated with better outcomes ($P<0.0001$) until 2 years from surgery when the survival rate became comparable to patients who did not receive adjuvant chemotherapy ($P=0.30$; Fig. 3A). Adjuvant radiation was associated with better 5-year survival (Fig. 3B) compared to patients who did not receive radiation ($P=0.003$). Surgery with any form of adjuvant therapy was associated with a trend of better 5-year survival compared to patients who received surgery alone (41.2% vs. 32.7%, $P=0.051$) with median survival 35.1 vs. 25.1 months, respectively (Fig. 3C).

On multivariable analysis of resected patients, younger age, low grade (well- or moderately differentiated) tumors, and negative resection margins (R0 vs. R1/R2) were independent prognostic factors (Table 4). There was no significant difference in survival between R1 and R2 resections ($P=0.98$). Adjuvant chemotherapy and/or radiation were not associated with better outcomes. Tumor size and T classification were examined separately and were also not independent predictors of survival. Nodal involvement was also not associated with survival. When grade was excluded from the model, T classification, tumor size, and nodal status remained nonsignificant predictors of survival.

Discussion

ACC is a rare tumor accounting for less than 1% of pancreatic cancers. It has a unique clinical presentation initially characterized by Berner in 1908.[20] Classically, patients are Caucasian males who present in their sixth or seventh decade with bulky tumors in the head of pancreas, although lesion topography may include the body or tail of the pancreas. Patients typically present with abdominal pain as opposed to painless obstructive jaundice,[21–23] the latter being more typical of a ductal adenocarcinoma of the head of pancreas. A small subgroup of ACC has been shown to actively secrete pancreatic enzymes. In extreme cases, patients manifest a syndrome characterized by systemic fat necrosis.[24] Pathologically, these tumors must be differentiated from tumors with endocrine or mixed endocrine differentiation which have a better prognosis.

Because of the rarity of ACC, large retrospective institutional series are not readily available to draw conclusions of sufficient power to generate meaningful hypotheses regarding outcomes and treatments of patients with ACC. By using the NCDB in this study, we were able to examine a large population of ACC to determine whether unique aspects of ACC could differentiate it from DCC and assess differences in survival of ACC compared to DCC.

The findings of our study are that patients were more likely to have ACC than DCC if they were male, white, had larger tumors, or lesions in the tail of the pancreas. Because pathology rarely provides a diagnosis of ACC preoperatively, a diagnosis of ACC should be considered in patients who fit this profile. Although ACC has often been characterized as having a poor prognosis,[2,5] our findings suggest that ACC is associated with improved stage-specific survival compared to DCC. Furthermore, patients with ACC are more than twice as likely to undergo resection than patients with DCC.

Table 3 Tumor Characteristics and Treatments of Resected Patients

	Acinar cell carcinoma	Ductal cell adenocarcinoma	Significance
Number of patients	333	62,167	
Median tumor size (IQR) cm	5.5 (3.5–9.0)	3.2 (2.5–4.5)	$P<0.0001$
T Classification			$P<0.0001$
T1	3.9%	10.7%	
T2	34.5%	18.8%	
T3	38.4%	44.0%	
T4	14.1%	12.4%	
Unknown	9.0%	14.1%	
Nodal metastases			$P<0.0001$
N0	60.1%	41.9%	
N1	32.1%	48.5%	
Unknown	7.8%	9.6%	
Distant metastases			$P=0.45$
M0	87.4%	90.4%	
M1	12.6%	9.6%	
Grade			$P<0.0001$
Well/moderately differentiated	25.5%	50.7%	
Poorly differentiated	22.8%	30.0%	
Unknown	51.7%	19.2%	
Location within pancreas			$P<0.0001$
Head	40.2%	68.7%	
Body	7.5%	5.6%	
Tail	30.9%	9.3%	
Other/diffuse/NOS	21.3%	16.4%	
Margins			$P=0.019$
R0	64.3%	55.9%	
R1	11.4%	12.7%	
R2	7.5%	10.2%	
Unknown	16.8%	21.2%	
Surgical procedure			$P<0.0001$
Pancreaticoduodenectomy	41.1%	57.8%	
Distal pancreatectomy	22.2%	6.7%	
Total pancreatectomy	9.9%	7.7%	
Other/NOS	26.8%	27.8%	
Treatment			$P=0.59$
Surgery only	57.1%	53.8%	
Surgery and chemotherapy	9.9%	9.4%	
Surgery and radiation	3.0%	4.8%	
Surgery and chemoradiation	30.0%	32.1%	

IQR interquartile range, *NOS* not otherwise specified

Long term survival of patients with ACC is predicted by younger age, lower grade tumors, and negative resection margins. Tumor size or T classification and nodal involvement were not independent predictors of survival. Thus, regardless of tumor size or T classification, patients with ACC should undergo surgical resection. Similar to DCC, the surgeon's contribution to long-term survival in patients with ACC is aggressive surgical resection with a goal of achieving R0 margins of resection.

Determining the effectiveness of adjuvant therapy using retrospective data from the NCDB is confounded by indication and selection bias. Adjuvant therapy in our study was not associated with better outcomes in patients with ACC on multivariable analysis. A recent institutional series from Johns Hopkins suggested that neoadjuvant chemoradiotherapy effectively downstaged four patients so they were amenable to surgical resection.[7] A multi-institutional series which included Indiana University patients also contained patients who were effectively downstaged by neoadjuvant chemoradiotherapy.[8] As endoscopic ultrasound-guided core biopsy of the pancreas becomes more common, a diagnosis of ACC may be increasingly appreciated prior to surgical resection which may facilitate enrollment in prospective neoadjuvant protocols and our understanding of the role of neoadjuvant chemoradiotherapy in this unusual pancreatic cancer.

Large-scale database studies such as ours give important information regarding expected survival, help understand

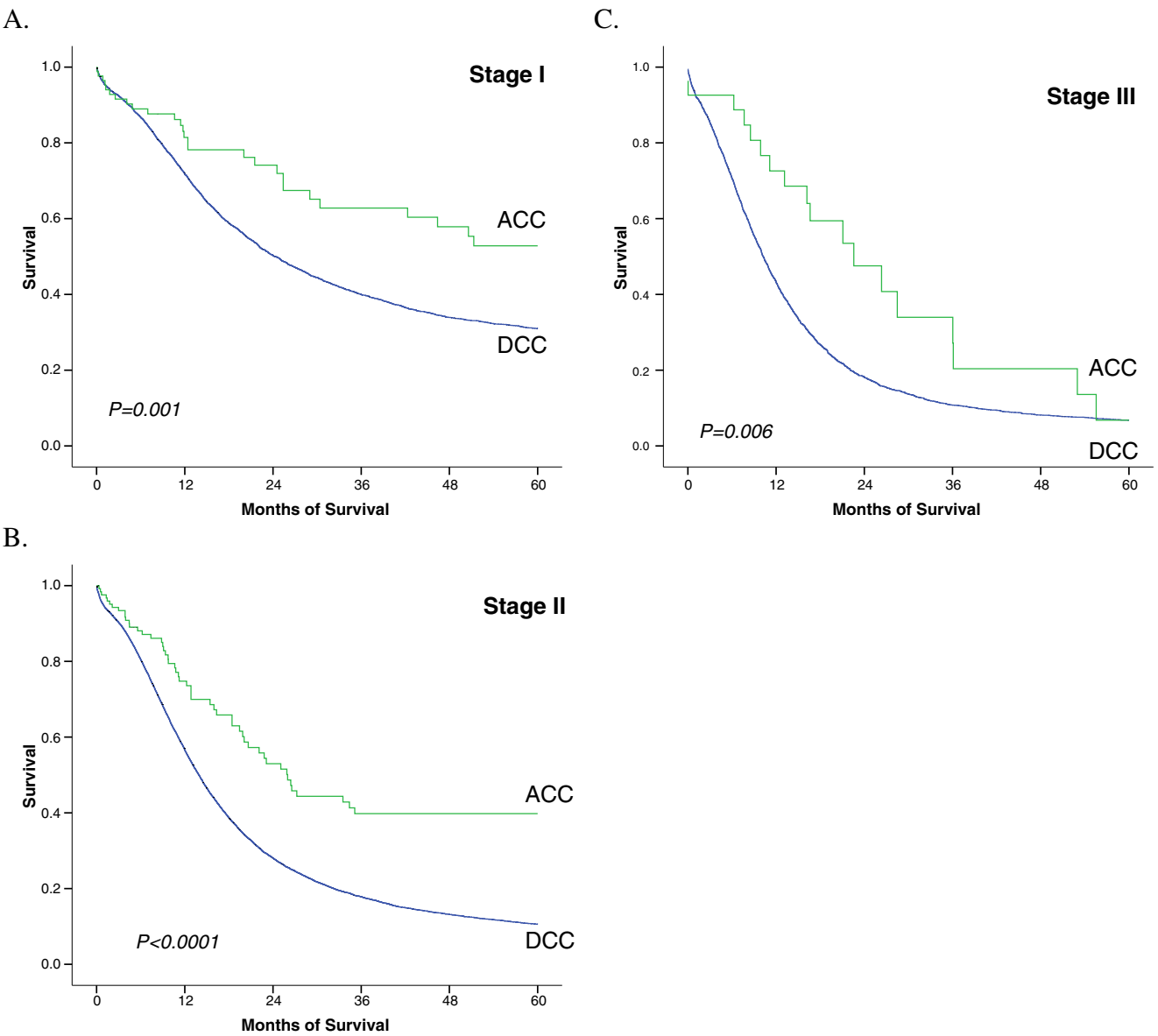

Figure 1 Five-year stage-specific survival after resection for ACC compared to DCC.

accuracy of staging, and allow for uniform stratification of patients in multi-institutional clinical trials. However, there are limitations that should be considered. First, these 865 ACC patients were treated at multiple hospitals over many years, and as a result, a detailed pathologic review was not feasible. Although we excluded neuroendocrine tumors, there may be some ACC patients in this study with mixed tumors, though the overall incidence of 0.5% is lower than in large institutional series, suggesting that the designation of ACC in these instances may be appropriate. Moreover, if a pathologist is classifying a tumor as an ACC, it is likely that they have a better understanding of the pathologic characteristics of these malignancies. Moreover, the nodal positivity and margin-positive resection rates are lower for DCC than prior single-institution reports suggesting considerable variability in surgical and pathologic quality at these institutions which may not specialize in pancreatic cancer. Secondly, certain data are not available in cancer registries such as the specific type of chemotherapy administered or details regarding radiation therapy. Thus, institutional and multi-institutional reports of ACC remain important to perform more detailed analysis of presentation, pathology, natural history, and specific treatment-related outcomes of ACC.

Information on ACC remains limited, but it appears from the NCDB data that like DCC, aggressive surgical resection should be performed in fit patients with localized tumors. The role of adjuvant therapy is unclear due to the inherent selection bias, but at the least, patients do not appear to have worse outcomes with adjuvant therapy which should encourage enrollment in prospective protocols going

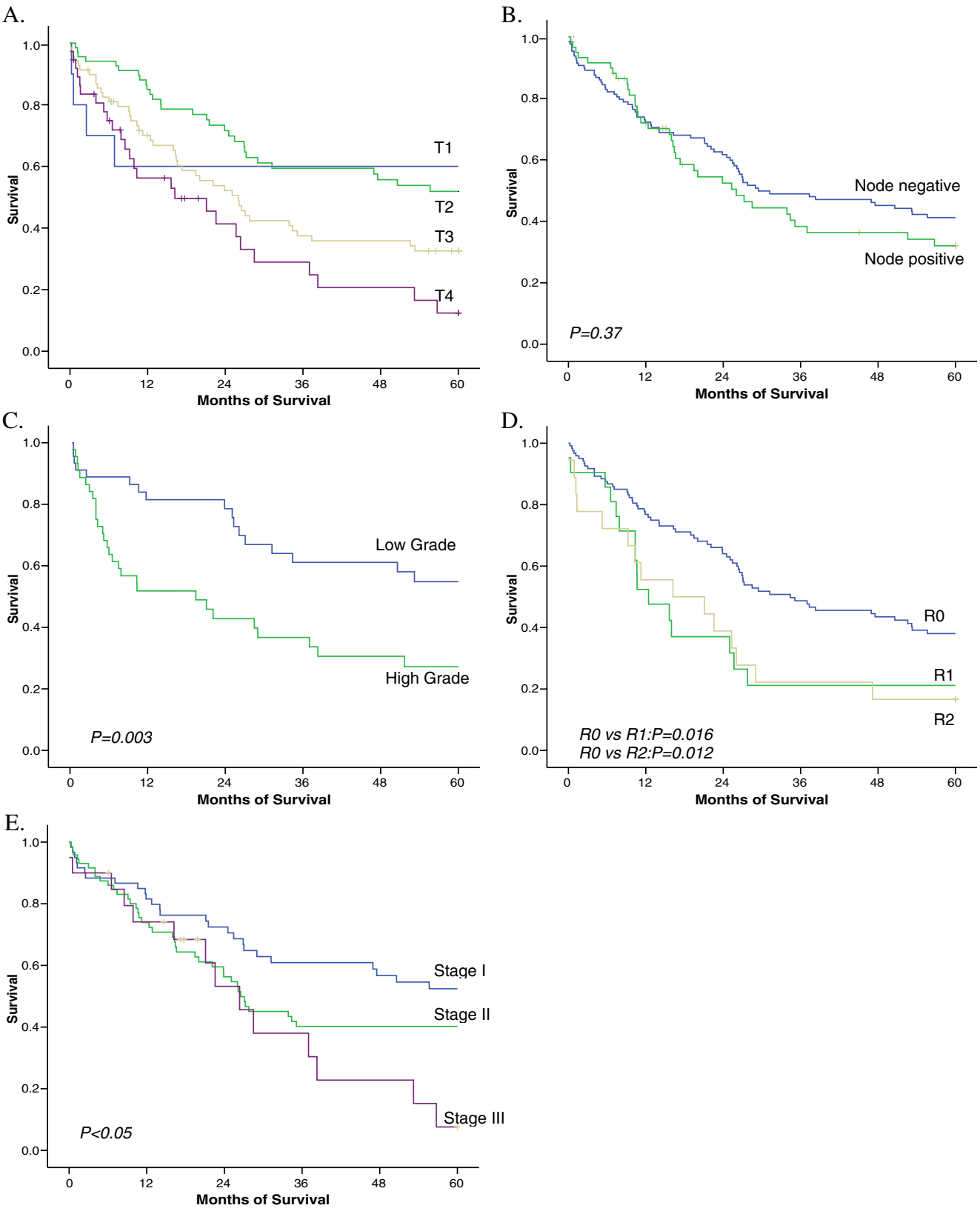

Figure 2 Five-year survival after resection for ACC by **A** T classification, **B** nodal involvement, **C** tumor grade, **D** margin status, and **E** overall AJCC Stage.

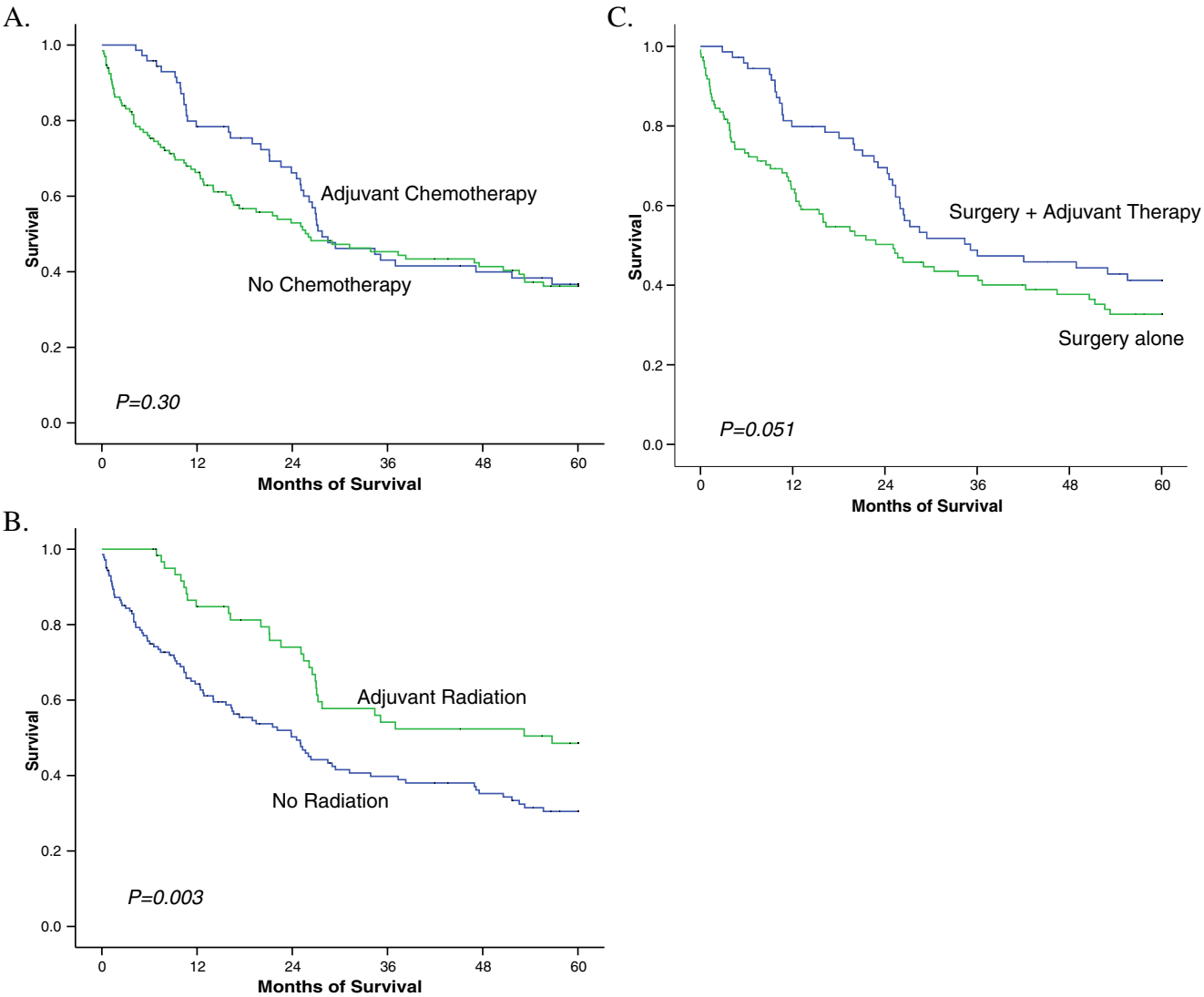

Figure 3 Five-year survival for resected ACC patients receiving **A** adjuvant chemotherapy, **B** adjuvant radiation, and **C** adjuvant treatment (chemotherapy and/or radiation).

Table 4 Factors Associated with Long-Term Survival after Resection of Acinar Cell Carcinomas

	Hazard ratio (95% confidence interval)	Significance
Age at diagnosis (continuous)	1.02 (1.00–1.03)	*P*=0.025
Grade		
Well/moderately differentiated	1.0 (Referent)	*P*=0.028
Poorly differentiated	1.89 (1.07–3.35)	
Margin status		
R0	1.0 (Referent)	*P*=0.013
R1/R2	1.78 (1.13–2.80)	

Hazard ratios >1.0 indicate a higher risk of death within 5 years. Factors not significant in the model include T classification, nodal status, and distant metastases; 204 cases had sufficient follow up to be included in the Cox model

forward. Since surgical resection appears to be the most effective treatment, patients with locally unresectable or metastatic tumors should be considered for neoadjuvant protocols in an attempt to downstage disease to make them candidates for surgical resection.

Acknowledgements KYB is supported by the American College of Surgeons, Clinical Scholars in Residence program.

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J Gastrointest Surg (2008) 12:2087–2096
DOI 10.1007/s11605-008-0713-6

Mechanisms of Primary Operative Failure and Results of Remedial Operation in Patients with Chronic Pancreatitis

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Received: 21 May 2008 / Accepted: 18 September 2008 / Published online: 10 October 2008

Abstract
Introduction Resection and drainage operations achieve long-term pain relief in approximately 85% of patients with chronic pancreatitis (CP). In patients who develop recurrent pain, a few data exist on the long-term results of remedial operations.
Materials and methods Over an 18-year period (1988–2006), 316 patients with CP had primary resection or drainage operations at our institution. Thirty-nine developed recurrent pain and were treated by a remedial resection or drainage operation. Patient demographics, time to symptom recurrence, radiographic anatomic abnormalities, type of remedial operation, postoperative morbidity, and long-term outcomes were analyzed.
Results Thirty-nine patients, 56% female with a mean age of 41 years (range 16–61 years) had either remedial resection: total pancreatectomy (TP; $N=8$), pancreaticoduodenectomy (PD; $N=6$), distal pancreatectomy (DP; $N=5$), or drainage operation: duodenal preserving pancreatic head resection (DPPHR; $N=8$), revision of pancreaticojejunostomy ($N=12$). TP achieved pain relief in 88% with postoperative complications greater than or equal to grade III in 38% and diabetes in 100%. Drainage operations achieved pain relief in 67% of patients with postoperative complications greater than or equal to grade III in only 8%. Partial parenchymal resections (DPPHR, PD, DP) as a remedial procedure achieved pain relief <50% of the time.
Conclusion Drainage procedures, when anatomically feasible, are the preferred reoperation to treat patients with recurrent pain after failed primary operation for chronic pancreatitis.

Keywords Chronic pancreatitis · Pancreaticoduodenectomy · Pancreaticojejunostomy · Duodenal-preserving pancreatic head resection · Distal pancreatectomy · Remedial operation

Presented at the 49th annual meeting of the Society for Surgery of the Alimentary Tract, May 20, 2008, San Diego, California.

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Introduction

Chronic pancreatitis (CP) is a vexing disease affecting between 5.6–24.2 million people in the United States, yet its precise etiology, pathogenesis, and clinical course remains ambiguous.[1,2] Current treatment algorithms recommend the selective application of surgery (either resection or drainage) to patients when medical treatment has failed or when structural complications of the disease (e.g., biliary stricture, duodenal stricture, mesenteric venous hypertension, symptomatic pseudocyst) develop.[3,4] Primary operations, when properly applied, achieve long-term pain relief in approximately 85% of patients.[5–9] However, it is noteworthy that 15% of patients with chronic pancreatitis have recurrent pain following primary operation and that this lack of success is relatively consistent across all large surgical series regardless of the etiology of chronic pancreatitis, type of primary operation applied (resection

vs. drainage), or geographic region in which the operation was performed.[4–9] Despite this universal experience of patients with CP having recurrent pain following primary operation, a few studies have carefully analyzed the operative indications and results following remedial surgery in this setting.[10–14]

This paper analyzes our 18-year single institutional experience applying reoperation to 39 patients with recurrent pain following initial operation for chronic pancreatitis. We investigated patient demographics, etiology of chronic pancreatitis, initial operative procedure, preoperative narcotic analgesic use, time to symptom recurrence, anatomic abnormalities identified on radiographic imaging, type of remedial operation, postoperative morbidity and mortality, and long-term pain relief.

Materials and methods

We retrospectively queried our pancreatic surgery database for all operations done between January 1, 1988 and July 1, 2006 for the indication chronic pancreatitis (ICD-9=577.8). Three hundred sixteen patients were identified whose primary operations included: pancreaticoduodenectomy (PD) in 100, duodenal preserving pancreatic head resection (DPPHR) in 53, lateral pancreaticojejunostomy (LPJ) in 51, and distal pancreatectomy (DP) in 112. PD was carried out as previously described.[15] Reconstruction of the pancreaticojejunostomy was done using a two-layer, end-to-side technique utilizing a duct to mucosa anastomosis (Warren–Cattell anastomosis) using six interrupted 5-0 absorbable monofilament sutures. The anastomosis was completed with an outer layer of interrupted seromuscular to pancreatic capsule 3-0 silk sutures. DPPHR was done following the methods of Beger[5] and Frey.[6] In both operations, the longitudinal pancreaticojejunostomy is constructed in two layers with an inner layer using a running 3-0 absorbable suture. A duct-to-mucosa anastomosis is not always possible, particularly in the cored-out sections of the pancreatic head where a shell-like capsule is encountered. In this situation, sewing the jejunum's full thickness to the pancreatic capsule usually allows for adequate drainage and decompression.[5,6] LP was carried out using a two-layer anastomotic technique with an inner layer of running 3-0 absorbable suture and outer layer of 3-0 silk from the seromuscular layer of the jejunum to pancreatic capsule. None of these anastomoses were stented.

From this cohort, 39 patients (12%) developed recurrent symptoms of abdominal pain (N=32) or episodes of pancreatitis (n=7) with radiographic imaging showing an anatomic structural abnormality amenable to reoperation. All patients had reoperation by one of the two co-authors of this paper (JAM, TJH) using either resection [total pancreatectomy (TP), PD, DP] or drainage operations [DPPHR, revision of pancreaticojejunostomy (RPJ)]. Prior approval for this investigation was obtained through the IUPUI Institutional Review Board (0707-80) and patient medical records including consultation notes, admission history and physical exams, operative reports, clinic notes, radiographic imaging reports were retrospectively reviewed. Follow-up was done using clinic visit notes, direct mailing, query of the social security death database, or phone calls. Follow-up was completed to March 2008.

To evaluate the appropriateness of the primary operation, four pancreatic surgeons who are co-authors of this study (TJH, NJZ, HL, MSB) independently evaluated a scripted clinical history and pertinent radiographic imaging information obtained from the patients' medical records just prior to the primary operation. Participants then voted, based on the information given, whether the primary operation was an appropriate or inappropriate operative strategy based on the size and configuration of the pancreatic duct, presence and location of inflammatory lesions, evidence of biliary stricture, and overall gland morphology (Fig. 1). Three of the four reviewing surgeons had to be in agreement to classify an operation as either appropriate or inappropriate. In no case was arbitration or re-voting necessary to obtain a 75% consensus. In one patient, all reviewers were in agreement that, given the information available in the script, no decision could be made.

All 39 patients had radiologic imaging to investigate the etiology of their recurrent symptoms following their primary operation. Cross-sectional imaging with either computer tomography (CT) (N=35) or magnetic resonance imaging (MRI; N=4) was applied. In addition, pancreatic and biliary ductography was performed in a selective manner using either endoscopic retrograde cholangiopancreatography (ERCP; N=28), magnetic resonance cholangiopancreatography (MRCP; N=16), or endoscopic ultrasound (EUS; N=8).

Retrospective review of outpatient clinic, hospital, and consultant notes were used to identify the anatomic structural abnormalities that were felt to be responsible for the patient's recurrent abdominal pain. These were divided into three categories: pancreatic duct or pancreaticojejunostomy strictures (N=16), biliary strictures (N=7), or parenchymal disease progression (N=16). In eight patients with presumed strictures of the pancreaticojejunostomy following PD, secretin-stimulated MRCP (N=4) or EUS (N=4) was performed.[16,17] During both secretin-stimulated EUS and MRCP, the pancreatic duct was identified, and baseline main pancreatic duct size was measured in the body region of the gland. Seventy-five units of synthetic porcine secretin (ChiRhoClin, Silver Spring, MD, USA) was slowly administered over 1 min intravenously to dilate the

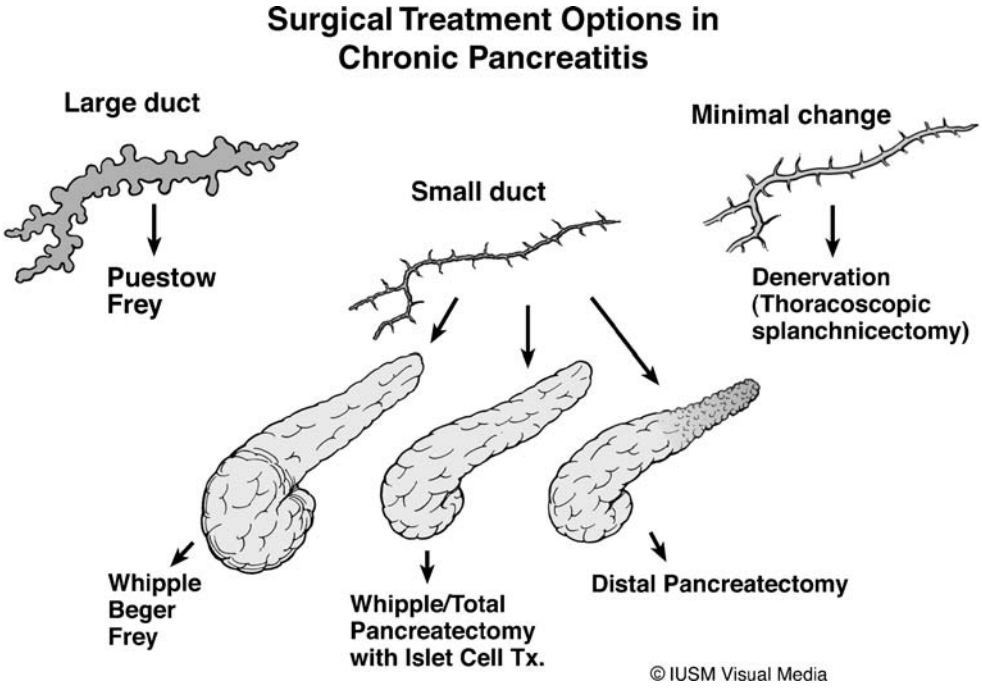

Figure 1 Types of operation based upon anatomic and morphologic variables in chronic pancreatitis.

visualized main pancreatic duct. Serial measurements of duct size were made every minute and recorded for 15 min. A positive secretin-stimulation test indicating functional duct obstruction was defined when the diameter of the pancreatic duct, after maximal dilatation in response to secretin, did not return to within 25% of its measured baseline within 15 min.

Symptomatic biliary strictures were defined as a >50% reduction in cross-sectional diameter of the intrapancreatic portion of the common bile duct associated with proximal duct dilatation, an elevated serum alkaline phosphatase level (>2× the upper limit of normal), and in four patients, symptom improvement with endoscopic stenting. Disease progression was defined as radiographic evidence of new inflammatory foci, increased pancreatic ductal or parenchymal lithiasis, or fibrotic changes in a portion of the gland that had not been surgically manipulated compared to prior radiographic imaging studies.

Postoperative morbidity in this series was broken down into perioperative complications and long-term endocrine and exocrine dysfunction. Perioperative complications were classified by the grading system developed for pancreatic surgery by DeOliveira and colleagues stratifying severity from I–V[18] [Table 1]. Postoperative pancreatic fistulas were

Table 1 Classification of Surgical Complications Adopted for Pancreatic Surgery[17]

Grade	Definition
I	Any deviation from the normal postoperative course without pharmacologic and radiological interventions; allowed therapeutic regimens are: antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy; this grade also includes wound infections opened at the bedside
II	Requiring pharmacologic treatment with drugs other than ones allowed for grade 1 complications; blood transfusions and TPN[a] are also included
III	Requiring surgical, endoscopic, or radiologic intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)[b] requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death
Suffix "d"	Complication at the time of discharge

[a] Note regarding DGE: The insertion of a central line for TPN or NJ tube by endoscopy is a grade IIIa. However, if a central line is still in place or a feeding tube has been inserted at the time of surgery, then TPN or enteral nutrition is a grade II complication
[b] Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding TIA's

graded for severity utilizing the International Study Group for Pancreatic Fistula guidelines.[19] For endocrine function, medical records were analyzed to find each patient's status with respect to preoperative insulin and oral diabetic medication, and these were considered as the patient's baseline. Postoperative diabetic medication use was defined as stable doses of drugs taken during the patient's long-term follow-up. Diabetic medications taken in the hospital during the perioperative period which were not continued as an outpatient were excluded. Blood glucose (BG) levels were recorded within these time intervals, and average BG values for both preoperative and postoperative periods were analyzed. Mean BG values less than 150 mg/% were accepted as adequate medical treatment. Patients were categorized as nondiabetic preoperatively if they had a mean BG value less than 150 mg/% and were taking no oral hypoglycemic medications. Worsening endocrine function was defined as patients requiring an increase in their medication requirements: e.g., from a nondiabetic to oral hypoglycemics, from oral hypoglycemics to requirement for insulin, or from once a day insulin therapy to multiple daily doses. For exocrine function, new treatment with exogenous pancreatic enzyme preparations was considered evidence of exocrine insufficiency. Patient weights recorded during the postoperative follow-up period were used as a surrogate for adequacy of endocrine and exocrine function.

Pain was assessed by documenting the patients' stable home narcotic pain medication regimens (if any) prior to the time of reoperation and then reassessing the patients stable narcotic pain medication requirements in the postoperative follow-up period. All narcotic pain medications were normalized and expressed as an equivalent dose of morphine (EDM). Excluded were any medications used during the patient's perioperative hospital admissions which were not continued during long-term follow-up. An increasing narcotics profile was defined as one in which a patient's narcotic pain medications had an increase in dosage (i.e., milligrams), administration rate (BID to TID), or in cases where a stronger opioid agonist (higher EDM) was required.

Continuous variables were summarized by mean and SD and categorical variables were summarized by frequency and percentage. Fisher's exact test was used to compare categorical variables. Kruskal–Wallis test was also conducted to compare continuous outcomes. All analyses were conducted using SAS 9.1 (SAS, Cary, NC, USA).

Results

Complete follow-up information was available on 35 patients with a mean duration of follow-up of 50 months (range 1–133 months). Four patients (10%) were lost to follow-up. Thirteen patients died during follow-up; 1-, 5-, and 10-year mortality was 8%, 18%, and 33%, respectively. There were 16 males (41%) and 23 females (59%) with a median age at the time of their remedial operation of 41 years (range 16–61 years). Etiologies of chronic pancreatitis were: ETOH in 17 (43%), pancreas divisum in ten (26%), idiopathic in nine (23%), and familial in three (8%). There were no significant differences in the etiology of pancreatitis at our institution between patients who had primary operation and those who had reoperation (data not shown). The incidence of remedial surgery following primary operation was 21% (11/53) for DPPHR, 18% (9/51) for lateral pancreaticojejunostomy, 10% (10/100) for PD, and 8% (9/112) for DP.

The anatomic abnormalities found in patients with recurrent pain following primary operation are shown in Table 2. While a higher percentage of patients treated by primary drainage operations LPJ (9/51, 18%) or DPPHR

Table 2 Anatomic Abnormalities Found on Radiographic Imaging and Time to Pain Recurrence in Patients with Chronic Pancreatitis Following Primary Operation

Primary operation	Overall failure rate	Anatomic abnormality			Time to pain recurrence (months)[a]
		PJ stricture	CBD stricture	Disease progression	
PD	10/100 (10%)	7 (70%)	0	3 (30%)	28±45
DPPHR	11/53 (21%)	4 (36%)	3 (27%)	4 (36%)	22±30
DP	9/112 (8%)	2 (22%)	2 (22%)	5 (56%)	16±11
LPJ	9/51 (18%)	3 (33%)	2 (22%)	4 (44%)	15±9
Totals	39/316 (12%)	16	7	16	
p-values[b]	0.06	0.39			0.77

PD pancreaticoduodenectomy, *DPPHR* duodenum-preserving pancreatic head resection, *DP* distal pancreatectomy, *LPJ* lateral pancreaticojejunostomy

[a] Data expressed as mean±SD

[b] For comparison of overall rate, anatomic abnormality and mean time to pain recurrence among the four primary operation types. Fisher's exact test and Kruskal–Wallis are used to categorical variables and continuous variables, respectively

(11/53, 21%) developed recurrent pain than patients treated by primary resection operations such as PD (10/100, 10%) or DP (9/112, 8%), these differences were not statistically significant ($p=0.06$). The mean time to pain recurrence was 15–28 months for the four types of primary operations. There is no significant difference in time to pain recurrence among the four groups ($p=0.77$)

Pancreaticojejunostomy (PJ) strictures were the most common anatomic abnormalities associated with recurrent pain in this series. Seven percent (7/100) following primary PD operations done at our institution had this associated abnormality concurrent with the development of recurrent pain in the postoperative period. Of the 11 patients who developed recurrent pain following DPPHR, PJ strictures were found in four (36%). Interestingly, of the five patients with recurrent pain after Frey-type DPPHR, three (60%) were attributed to CBD strictures while no patient with recurrent pain treated primarily by the Beger-type DPPHR was found to have this anatomic abnormality. PJ stenosis was observed in a substantial number of patients who developed recurrent pain following both the Beger- (4/6, 67%) and Frey- (2/5, 40%) type DPPHR. Disease progression was the most common anatomic abnormality identified by radiographic imaging in patients following DP (5/9, 56%) while the most common radiographic abnormalities following LPJ were ductal strictures (PJ=3/9, 33% and CBD=2/9, 22%).

Reoperation was targeted at the anatomic abnormalities found on radiographic imaging. When these were grouped as either resection (e.g., TP, PD, and DP) or drainage (e.g., DPPHR, PJR) procedures, this relationship is highlighted (Table 3). For PJ strictures, eight (50%) had anastomotic PJ revisions and in the four resections that were done, three were PD targeted at a poorly drained head following LPJ. In patients with CBD strictures, all reoperations (one PD, three DPPHR, and three PJR) were directed at relieving this structural anatomic abnormality. The most heterogeneous group of patients were those identified on imaging to have disease progression with increased gland fibrosis, distortion, pancreaticolithiasis, intraparenchymal stones, and inflammation. The majority of these patients, 11/16 (69%), were treated by resection. Of the five patients treated by drainage, four (80%) had composite operations which included partial head resection utilizing DPPHR.

Overall pain improvement following reoperation was observed in 23 patients (59%), no change occurred in five patients (13%), and pain worsened in 11 patients (28%) at a mean follow-up period of 50 months (range 1–133). Occupational rehabilitation was possible in 19 (49%) of patients, while nine (23%) were found to meet requirements as legally disabled. Pain improvement occurred in 7/8 of the patients (88%) following total pancreatectomy and in 8/12 (67%) of patients following PJ revision (Table 4). Lesser magnitudes of resection, PD and DP, resulted in pain improvement in 50% and 40% of patients, respectively. DPPHR, when used as a remedial operation, was effective in pain improvement in only 38% of patients. Remedial resection operations were generally accompanied by a higher rate of serious postoperative complications (≥Grade IIIa) than remedial drainage operations, which reaches statistical significance ($p=0.03$). While pancreatic fistulae were more common in the remedial drainage operations, two thirds were simple type A fistulae that resolved without difficulty. Aggressive resections that involved total pancreatectomy had a universal (100%) requirement for increasing diabetic management, and one patient had new onset steatorrhea requiring enzyme supplementation. In contrast, PJ revision resulted in only two patients (22%) requiring increasing DM management in the postoperative period.

Table 3 Remedial Operations, Grouped as Either Primarily Resection or Drainage Procedures, and their Application to the Anatomic Abnormalities Found in Patients with Recurrent Pain Following Primary Operation

Anatomic [*,a] Abnormality	Number (*N*)	Resection			Drainage	
		TP	PD	DP	DPPHR	PJR
PJ Stricture	16	2	2	3	1	8
CBD Stricture	7	0	1	0	3	3
Disease progression	16	6	3	2	4	1
Totals		8	6	5	8	12

TP total pancreatectomy, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *DPPHR* duodenum-preserving pancreatic head resection, *PJR* pancreaticojejunostomy revision

[*] $p=0.04$; Fishers exact test of the independence of anatomic abnormality and specific remedial operation (TP, PD, DP, DPPHR, and PJR)

[**] $p=0.06$; Fisher's exact test of the independence of anatomic abnormality and type of operation (resection vs. drainage)

Discussion

While the goal of most operative interventions is to achieve a desired outcome with a high degree of precision, alleviating abdominal pain in patients with chronic pancreatitis at times seems more art than science. Standard teaching of operative selection is based on two generally accepted theories of pain: (1) increased pancreatic parenchymal pressures caused by pancreatic duct hypertension due to flow obstruction caused by strictures, pancreaticolithiasis, or fibrosis[20] and (2) inflammatory cell infiltration, loss of myelin sheath, and persistent neuritis of the sensory nerves surrounding the pancreas due to toxic substances secreted during episodes of pancreatitis.[21,22] Dovetailing with these two mechanistic hypotheses are clinical data in

Table 4 Outcomes from Remedial Operations in 39 Patients with Chronic Pancreatitis Who Developed Pain Recurrence Following Primary Operations

Remedial operation	Number (*N*)	Pain improvement	Pancreatic fistula	New DM Tx.	New enzyme Tx.	Complication ≥ IIIa
Resection						
TP	8	7 (88%)	0	7/7 (100%)	1/1 (100%)	3 (38%)
PD	6	3 (50%)	1 (17%)[a]	3/5 (60%)	0/2	2 (33%)
DP	5	2 (40%)	0	1/5 (20%)	0/2	3 (60%)
Total	19	12 (63%)	1 (5%)	11/17 (70%)	1/5 (20%)	8 (42%)
Drainage						
DPPHR	8	3 (38%)	1 (13%)[a]	2/7 (28%)	0/2	2 (25%)
PJR	12	8 (67%)	2 (17%)	2/9 (22%)	0/4	1 (8%)
Total	20	11 (55%)	3 (15%)	4/16 (25%)	0/6	3 (15%)
P[b]		0.19	0.89	0.57[d]	0.09	0.31
P[c]		0.48	1	0.04	0.45	0.03

TP total pancreatectomy, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *DPPHR* duodenum-preserving pancreatic head resection, *PJR* pancreaticojejunostomy revision

[a] C grade pancreatic fistulas

[b] Fisher's exact test of independence of column variables and specific remedial operation (TP, PD, DP, DPPHR, and PJR)

[c] Fisher's exact test of the independence of column variables and type of operation (resection vs. drainage)

[d] TP is excluded because the operation will for sure lead to new DM treatment

different groups of patients with CP that lend support to these theories. The first group of patients are those with CP who express the phenotypic variant of a large, dilated pancreatic duct (chain of lakes) who are shown to have an excellent clinical outcome following pancreatic duct decompression through longitudinal pancreaticojejunostomy.[3,8] The second group of patients is those with CP who express the phenotypic variant of an enlarged, hypertrophic pancreatic head but small pancreatic duct. This group has excellent clinical outcomes following pancreatic head resection (Fig. 1).[3,7] Although pure variants of each type can be found, the vast majorities of patients with CP have a heterogeneous expression of these characteristics and are not easily categorized into large duct or small duct variants. Even when these anatomic and morphologic selection criteria are adhered to rigidly, approximately 15% of patients develop persistent or recurrent abdominal pain. This percentage is likely to increase as the period of postoperative observation lengthens.[7,23] When designing this study, there were two main goals we wished to accomplish: (1) anatomic structural abnormality determined by radiographic imaging in patients with pain recurrence following primary operation for chronic pancreatitis and (2) analyze the outcomes of remedial operations in these patients.

When an operation in patients with chronic pancreatitis fails to provide long-term pain relief, multiple factors may be implicated. Patient factors including persistent alcohol abuse, narcotic addiction, and severe depression often complicate interpretation of outcomes following surgery. Based upon individual patient's clinical history and their lack of in-hospital postoperative withdrawal symptoms, no patient in this study was known to be abusing alcohol at the time of their remedial operation. Narcotic addiction and depression are more difficult variables to tease out retrospectively. Identification and treatment of these factors often require a committed team of diverse health care professionals working together in a specialized unit.[24] Our institution, at the time these study patients were treated, did not have these specialized resources available. With regard to these issues, we again note the high long-term mortality rate in patients with chronic pancreatitis, 18% at 5 years and 33% at 10 years, in a relatively young cohort of patients (mean age 41 years) and a less than 50% rate of occupational rehabilitation in our series. High mortality rates have been identified in other surgical series of patients with chronic pancreatitis and have been attributed to lifestyle issues; however, the exact cause of death in many of these patients remains poorly defined.[7–9,25]

Technical factors and\or inappropriate operative strategies [e.g., choosing lateral pancreaticojejunostomy to treat small duct (<6 mm) chronic pancreatitis] have been suggested to be a major contributor to early postoperative failure.[10,12] In contrast, late postoperative failures are felt to be related to disease progression rather than clinical misjudgment. To retrospectively evaluate this issue, four pancreatic surgeon co-authors (TJH, NJZ, HL, and MSB) independently evaluated the scripted clinical history and radiographic imaging data from the primary operation in all patients in this study (Fig. 2). Overall, 14 primary operations (36%) were classified as having an inappropriate operative strategy. We found a steep increase in the percentage of operative strategies graded inappropriate (around 50%) in patients whose pain recurred within 19 months of their primary operation when compared to those whose pain recurred after 19 months of primary

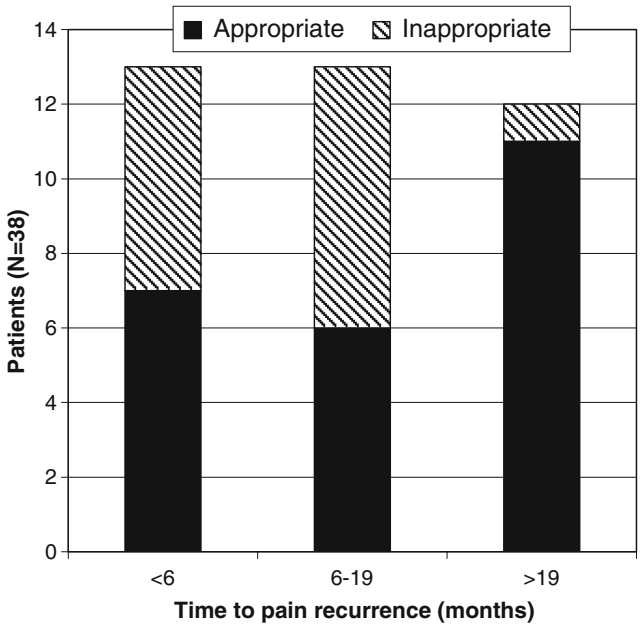

Figure 2 Relationship of the appropriateness of operative strategy used in the primary operation with the time to pain recurrence. Inappropriate operative strategies were significantly more common (p=0.03) in patients whose pain recurred within 19 months of their primary operation when compared to those whose pain recurred after 19 months of primary operation. Additionally, the median time to pain recurrence significantly longer for appropriate primary operation compared to inappropriate ones (p=0.04).

operation, and this difference is statistically significant (p=0.03). In addition, the median time to pain recurrence is also higher for appropriate primary operation compared to inappropriate ones (p=0.04). The most common inappropriate operative strategies identified were: (1) application of a lateral pancreaticojejunostomy to a pancreatic duct <8 mm in cross-sectional diameter (N=5), (2) inadequate treatment of a concomitant biliary stricture during pancreatic resection or drainage (N=5), and (3) distal pancreatectomy in patients with evidence of concomitant head disease (N=3). When applying rigid anatomic selection criteria retrospectively, it must be conceded that while most authorities agree that a pancreatic duct should be at least 8 mm in size for a successful long-term outcome from LPJ, successful results have been published in patients with smaller pancreatic ducts.[26] Furthermore, innovative investigations trying to extend the benefits of pancreaticojejunostomy (technically easier operation, lower perioperative morbidity, less endocrine and exocrine insufficiency) to small duct variants of chronic pancreatitis have been attempted using wall-stent duct dilatation[27] or extended drainage by "V-shaped excision" of the anterior aspect of the pancreas.[28] These published experiences may have contributed to the extended application of a drainage procedure to a patient with a small pancreatic duct.

Disease progression was radiographically identified as new inflammatory foci, lithiasis, or fibrotic changes in the pancreas when compared to previous radiographic studies. In the nine patients in this series whose primary operation was distal pancreatectomy, average time to pain recurrence was 16 months, and five of nine (56%) had radiographic evidence of disease progression. DP is a pure parenchymal resection without the need for pancreaticojejunostomy to establish pancreatic duct drainage. All remaining primary operations in this series had a pancreaticojejunal anastomosis of some form to reestablish pancreatic duct drainage. Having a PJ anastomosis puts patients at risk for developing anastomotic stricturing or stenosis which, based on the theory of ductal hypertension, can lead to recurrent pain. This mechanism of primary operative failure was found commonly in PD (70%), DPPHR (36%), and LPJ (33%) patients. In both Frey-type DPPHR and LPJ, the technique of pancreaticojejunostomy is done in a lateral orientation rather than end-to-side fashion making for a larger surface area and presumably less propensity for stricturing or stenosis.[6,8] Objective confirmation of stricturing of a pancreaticojejunostomy can be obtained using ERCP for lateral pancreaticojejunostomies such as those found in DPPHR or LPJ. In end-to-side pancreaticojejunostomies following PD, depending on whether the pyloro or gastrojejunostomy is done retrocolic or antecolic, the length of the biliopancreatic limb determines the difficulty of achieving endoscopic access. In this setting, secretin-stimulated EUS or MRCP is essential for making this diagnosis.[16,17]

A common mechanism of symptom recurrence is the progression of head disease in patients who undergo DPPHR or LPJ.[10,12] Inadequate resection of the pancreatic head during initial DPPHR can result in the reappearance or persistence of clinical symptoms. It has been emphasized that extending a LPJ into the head as close as possible to the duodenum, encompassing both the duct of Wirsung and Santorini in the anastomosis will minimize this occurrence, but prospective data on the benefit of this technical approach is lacking.[11] More commonly, remedial head resection (PD) has been used in this situation with good results in terms of pain relief but at the cost of a high postoperative complication rate.[10,12] Of interest in our series was the observation that of the five patients with recurrent pain after the Frey-type DPPHR, three (60%) were found to have evidence of biliary obstruction. In contrast, no patient after the Beger-type DPPHR (N=6) with recurrent pain had this mechanism. Recent observations on reinsertion of the common bile duct into the pancreatic resection cavity following DPPHR showed that symptomatic biliary strictures occurred in 18% of patients.[29] This particular technique was carried out in the primary operation of only one patient in this series. Failure

to remove sufficient tissue at the superomedial aspect of the resection near the intrapancreatic portion of the common bile duct or ischemia of the intrapancreatic portion of the distal common duct are speculated to be other possible etiologies for this now recognized complication of DPPHR.[29] PJ revision in patients with chronic pancreatitis who develop recurrent pain following a failed primary operation was the most common remedial operation applied in this setting and has been advocated by others.[11] It is straightforward and relatively well tolerated as reflected in the postoperative complication rate which was the lowest (8%) of all the remedial operations. PJ revisions were successful in decreasing narcotic pain regimens in 8/12 (67%) of the patients, and only two patients (22%) required expanded diabetic coverage postoperatively. These encouraging trends are somewhat intuitive as revisions do not remove glandular tissue.

TP to treat patients with chronic pancreatitis presents a unique set of issues. Because of the aggressive removal of pancreatic tissue, seven eighths (88%) of the patients were able to decrease their narcotic regimen, some substantially, but at the expense of all of the patients having an increase in their postoperative diabetic management. Furthermore, the only patient identified to have postoperative exocrine insufficiency came from this group of patients. From both an endocrine and exocrine standpoint, patients undergoing total pancreatectomy are dependent upon daily medications for life. Therefore, the patients who are selected to undergo this definitive procedure must be carefully selected. If not, one problem (pancreatitis) is traded for another, which is potentially more dangerous (poorly controlled diabetes).

The limitations of this study are its retrospective design, single institutional focus, and the small number of patients in each group available for analysis. Efforts were made to minimize the impact caused by the retrospective nature of our data by carefully defining our outcome measures prior to data gathering, but these actions can only approximate the precision of prospectively gathered information. Our patient population is slightly skewed when compared to other series of patients with chronic pancreatitis in that the majority of our patients are female (59%) and 26% have pancreas divisum as the etiology of their disease. Given this fact, generalizability of our findings to other populations of patients (male gender, alcoholic pancreatitis) may be limited.

Conclusion

Reoperation is beneficial in a select group of patients with recurrent symptoms following primary operation for chronic pancreatitis. In this subset of patients, drainage operations, when anatomically feasible, are the preferred approach.

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Discussion

David B. Adams, M.D. (Charleston, SC): Persistent pain and suffering afflicts patients who fail surgical management of chronic pancreatitis, which is a disease, as you know, characterized by heightened trypsinogen activation, exaggerated fibrosis, and neural hypersensitivity. Chronic pancreatitis has not one cause and is not one disease, thus, surgical treatment based upon phenotypic expressions of the disease is marked by frequent failure and the need for reoperation.

Now, postoperative pain, recurrent pancreatitis, exocrine and endocrine insufficiency, and death are reminders that chronic pancreatitis surgery is palliative surgery. You must understand then why I am so excited about today's report, which has the optimistic take-home message that remedial operations in patients with chronic pancreatitis work. Revising obstructed pancreatojejunal anastomoses and resecting damaged tissue with completion pancreatectomy are particularly successful. I am a great admirer of the patient and thoughtful work of Dr. Howard and Madura and thank them for bringing their art and science to this careful analysis, and for Dr. Browne, who did a superb job of presenting, I have three questions.

One, do you have any data on the cause of death in the patients who died in the follow-up period? Second, in the four patients lost to follow-up, which is a terrific follow-up rate, do you think they disappear from follow-up because they are doing well, doing poorly, or doing both? That is, are they dead? How many of these subjects do you think are patients not solely with pancreatitis but patients with concomitant visceral hypersensitivity disorder, which is related to their operative failure?

Again, thanks for a superb job.

Jeffrey S. Browne, M.D. (Indianapolis, IN): Dr Adams, on behalf of Dr. Howard, myself, and the other authors of the paper thank you for your questions. I will speak first regarding our mortality. In mentioning our 33% mortality, you noted our 1-, 5-, and 10-year mortality rates which were 8%, 18%, and 33%, respectively. We had one patient we know that died of pancreatic cancer. Concerning the other patients, in those we could not tract down by last known address or through their family members, we used the Social Security Death Index in order to evaluate our mortality rates, and unfortunately, cause of death is not a part of this index.

Concerning the four patients lost to follow-up, we believe they are alive as we have been unable to locate them through multiple attempts at following them through forwarding addresses, and they have not shown up on the Social Security Death Index.

Finally, concerning visceral hypersensitivity syndromes and their role in this patient population, this focuses on the difficulty in trying to decide whether the patient has a structural process or a functional one. A structural process would be amenable to reoperation; however, a functional problem, such as visceral hypersensitivity syndrome will generally not respond to reoperation. Twenty-three of the 39 patients in this series had pain improvement based on stable narcotic use in our study. This would imply that these patients had a structural problem amenable to revision. In contrast, 16 of the 39 patients experienced either no change in their narcotic requirements or worsening pain requiring an increase in medication usage. These patients may in fact have had a visceral hypersensitivity syndrome as the major component of their pain.

Matthew R. Walsh, M.D. (Cleveland, OH): I want to be clear how you define recurrent pain. Did none of these people have visual analog pain assessment scores? If recurrent pain was diagnosed by a change in morphine equivalents, how many people are actually still on any amount of narcotics? My other question is, have you considered, since your patients were not diabetic before their revisional surgery, of doing auto-islet cell transplantation?

Dr. Browne: In addressing your first question, we had only 40% of this entire population that had complete pre- and postoperative quality of life data available using the

EORTC instrument. Because of the incomplete nature of this assessment, we felt this data may be skewed to only patients who had a positive outcome and thus took the time to fill out this questionnaire and not be reflective of all the patients who underwent reoperation in this analysis. Looking for the next best objective measurement available, we felt that a patient's stable narcotic regimen, when assessed both pre- and postoperatively and normalized to equivalent doses of morphine over the entire population of this study, would be a reasonable objective measure of outcome. Any decreases in narcotic medication use was deemed as an improvement in pain, and we did not have a specific threshold in which change was felt to be significant or nonsignificant except in the context of the changes in the mean normalized doses of the populations studied.

Finally, there were eight patients in our series that had total pancreatectomy, and three of these patients had autologous islet cell transplant at the time of their resection.

Syed Ahmed, M.D. (Cincinnati, OH): I want to congratulate you on a very nice presentation. I have two comments. The first is, in our experience, we found that patients who have recurrent pain after primary surgery, the cause of pain is usually multifactorial. Sometimes it is due to stricture of the anastomosis or progression of disease. Oftentimes, though, they have concomitant bowel dysfunction as a source of pain. So the first question I have is, what kind of workup do these patients undergo to determine the etiology of the pain and to determine whether the pancreas was in fact the cause of pain?

The second is a comment. At Cincinnati, we perform auto-islet transplants for recurrent pain, and it has similar results. We found that in the approximately 105 patients for whom we have now performed that operation, there is about a 70% improvement in abdominal pain. I wish to advocate auto-islet transplantation as the procedure of choice in patients who have recurrent abdominal pain without any strictures or lateralization of disease.

Dr. Browne: In speaking to the multifactorial nature of recurrent disease, I can assure you that these 39 patients were carefully selected as having anatomic abnormalities on postoperative imaging which was amenable to remedial surgery. Of the 316 patients operated on for chronic pancreatitis in our experience, a percentage had recurrent pain but no targeted abnormality amenable to reoperation, and they were not included for analysis. Furthermore, the anatomic abnormalities found in patients with recurrent pain were also complex and multifaceted, for example, in the 16 patients with strictured pancreaticojejunostomies, five also had progressive head disease requiring with a Whipple or total pancreatectomy, and three others had progressive disease in the tail requiring distal pancreatectomy. So our experience, much like yours, is that even in patients with identifiable anatomic abnormalities after primary operation, their recurrent disease tends to be multifactorial.

In addressing your question about what imaging is necessary in this patient population, we use three things to evaluate pancreatic anatomy before reoperative surgery: number one is good cross-sectional imaging from CT or MR exam, number two is ductography of both the bile and pancreatic ducts utilizing either MRCP or ERCP, and number three is a thorough intraoperative evaluation at the time of remedial surgery.

Katie S. Nason, M.D. (Pittsburgh, PA): I just have a comment to make rather than a question. Use of the Social Security Index as your only source of vital statistics on patients is inherently faulty because the Social Security Index only includes patients who have had submissions for claims made. So they do not include all patients who have died, and in fact in our series, we found several patients who were dead and did not show up as dead in the Social Security Index but were confirmed dead by family members. So I think it is important to be cautious using the Social Security Index as your only source of vital statistics.

Dr. Browne: Thank you very much for that comment.

J Gastrointest Surg (2008) 12:2097–2102
DOI 10.1007/s11605-008-0704-7

Routine Liver Biopsy to Screen for Nonalcoholic Fatty Liver Disease (NAFLD) during Cholecystectomy for Gallstone Disease: Is it Justified?

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Received: 20 May 2008 / Accepted: 8 September 2008 / Published online: 30 September 2008

Abstract
Background Nonalcoholic fatty liver disease (NAFLD) and gallstone disease (GD) share common risk factors. There are no firm recommendations regarding screening of NAFLD in patients at risk. Our aim was to assess the prevalence of and factors associated with NAFLD in a cohort of patients operated for symptomatic GD and evaluate the usefulness of routine liver biopsy.
Methods Ninety-five consecutive patients underwent a liver biopsy at the end of a standard laparoscopic cholecystectomy for symptomatic GD. Clinical, biochemical, demographic, and anthropometric variables were obtained prospectively.
Results Fifty-two patients (55%) had biopsies compatible with NAFLD. These patients were classified according to the system proposed by Brunt et al. as follows: grade I, $n=27$ (52%); grade II, $n=15$ (29%); grade III, $n=10$ (19%). Two grade III patients had zone III focal perisinusoidal fibrosis and three had overt cirrhosis. Only 13% of subjects had a suspected diagnosis of NAFLD preoperatively. In multivariate logistic regression, only obesity was significantly associated with NAFLD. There were no complications or mortality.
Discussion Fifty-five percent of patients with GD have associated NAFLD. Awareness of this association may result in an earlier diagnosis. The high prevalence of NAFLD in patients with GD may justify routine liver biopsy during cholecystectomy to establish the diagnosis, stage, and possible direct therapy.

Keywords NAFLD · Liver biopsy · Gallstone disease · Risk factors · Screening · Prevalence

This work was presented at the Plenary Session of the 2008 Society of Surgery of the Alimentary Tract meeting in San Diego, CA, USA.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions and is emerging as a major health burden. The Dallas Heart study reported that one in three adults in the United States have steatosis.[1] This means that up to 70 million people currently have NAFLD in the USA.

NAFLD represents a spectrum of liver diseases characterized by excessive accumulation of fat in hepatocytes, mostly as macrovesicular steatosis and almost always associated with insulin resistance. In fact, NAFLD has been considered as the hepatic manifestation of the metabolic syndrome.[2] The hepatic histology can vary from steatosis alone to steatosis plus a degree of inflammation, ballooning of hepatocytes, and pericellular/perisinusoidal fibrosis (i.e., nonalcoholic steatohepatitis [NASH]). NASH has become a clinically relevant form of chronic liver

disease, and patients with this condition are at risk for the development of chronic liver disease and liver cancer.

NAFLD should be suspected in subjects with features suggesting the metabolic syndrome, such as overweight/obesity, insulin resistance, dyslipidemia, and hypertension. Other risk factors related to NAFLD are ethnicity, obesity phenotype, reduced physical activity, and high-fat diets. Interestingly, even though these risk factors are highly prevalent in the population, there are no recommendations for screening of NAFLD in high-risk patients. Noninvasive methods to diagnose NAFLD are unreliable and liver biopsy is the only method for assessing the presence and extension of this condition.[3] In general, liver biopsy is performed in patients who have suspected NAFLD for (1) confirming the diagnosis and stage of disease and (2) determining prognosis based on severity of fibrosis.[4] Firm recommendations of when to perform a liver biopsy in routine clinical evaluations are lacking.

Similar to NAFLD, gallstones disease (GD) is often associated with obesity, hypertriglyceridemia, insulin resistance, and type 2 diabetes mellitus.[5–8] Thus, it is reasonable to expect that patients with GD have a higher prevalence of NAFLD.[9–12] However, information related to this intriguing association is scarce.

In this study, our aim was to assess the prevalence of and factors associated with NAFLD in a cohort of patients operated on for symptomatic GD and to evaluate the usefulness of routine liver biopsy as a screening method. We also analyzed whether anthropometric, clinical, and biochemical parameters can be used to predict the presence of NAFLD in this population.

Methods

We prospectively evaluated consecutive patients referred for cholecystectomy due to symptomatic GD confirmed by ultrasonography between January 1, 2005 and June 30, 2006. The study was accepted by the internal review board and all patients were consented prior to enrollment. Demographics, anthropometric measurements, family history, risk factors, comorbid conditions, laboratory tests, alcohol ingestion, medication use, and abdominal ultrasonographic (US) findings were registered and analyzed.

Intravenous blood samples were collected from every patient after a 12-h fast and the following biochemical test were performed: complete blood count, glucose, creatinine, uric acid, blood urea nitrogen, total cholesterol, high-density lipoprotein cholesterol (HDL-C), glycated hemoglobin (Hb_{A1c}), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, total protein, globulins, and albumin. Serum markers of hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) were performed. Patients with a positive serology for HBV or HCV, those with a history of alcohol ingestion greater than 150 g/week, liver cirrhosis, autoimmune hepatitis, or other liver disease were excluded. Alcohol intake was assessed using a self-reporting validated questionnaire.

All patients underwent a wedge biopsy from the free border of the left liver lobe performed at the end of a standard laparoscopic cholecystectomy away from any area of surgical manipulation. Using standard laparoscopic scissors, a wedge-shaped section of liver was excised and retrieved with a grasper through the 10- to 12-mm subxiphoid trocar in order to minimize damage to the specimen. Hemostasis was secured by using monopolar electrocautery only after the specimen was obtained. All biopsies were deemed adequate for histological interpretation, reviewed, and graded by a single pathologist. Hematoxylin and eosin and Masson's trichrome stains were performed on all specimens. Those biopsies with NAFLD were classified according to the system proposed by Brunt et al.[13]

Descriptive statistics were used according to the type of variable measured. The odds ratio and its confidence interval were estimated at 95%. The statistical significance of the associations was evaluated by the χ^2 test, and in those cases in which the conditions for its performance were not fulfilled, Fisher's exact test was used. The level of statistical significance was fixed at 0.05 for the bimarginal null hypothesis. For continuous variables, Student's t test was performed. A multivariate analysis was also performed using a logistic regression (stepwise forward model). Statistical analysis was performed with SPSS 13 for Windows (SPSS, Chicago, IL, USA).

Results

Ninety-five patients were evaluated, 29 males (31%) and 66 females (69%). Mean age was 52.15±16.82 years (range 21–84 years). Forty-three subjects (45%) had a normal liver biopsy (group A). In the remaining 52 patients (55%), there were histological findings compatible with NAFLD (group B). According to the system proposed by Brunt et al., subjects in group B were staged as follows: grade I, n=27 (52%); grade II, n=15 (29%); grade III, n=10 (19%). Of the ten grade III patients, two had zone III focal perisinusoidal fibrosis and three had overt cirrhosis.

Sociodemographic characteristics and risk factors for NAFLD among groups are shown in Table 1. Group B patients were significantly older and had higher body mass index when compared to group A. Also, prevalence of obesity and dyslipidemia were significantly associated to group B subjects (Table 1). A family history of hypertension,

Table 1 Sociodemographic Characteristics and Risk Factors among Groups

	Group A n=43	Group B n=52	OR (CI)	p value
Sex, n (%)				
Male	14 (33)	15 (29)	0.83 (0.3–2.01)	0.69
Female	29 (67)	37 (71)		
Age (mean±SD)	48.13±14.8	55.6±17.9*	–	0.02
Body mass index (mean±SD)	26.5±3.1	28.8±4.9*	–	0.09
Waist, cm (mean±SD)	86.1±1.2	89.5±2*	–	0.001
Risk factors, n (%)				
Obesity	11 (25)	25 (48)*	2.69 (1.12–6.46)	0.04
Type 2 diabetes	4 (9)	9 (17)	2.04 (0.58–7.15)	0.40
Hypertension	9 (21)	19 (36)	2.17 (0.86–5.49)	0.15
Dyslipidemia	24 (56)	40 (77)	2.63 (1.09–6.37)	0.049
Family history, n (%)				
Obesity	13 (30)	42 (81)*	9.69 (3.75–25)	0.0001
Type 2 diabetes	30 (70)	41 (79)	1.61 (0.63–4.02)	0.43
Hypertension	3 (7)	21 (40)*	9.03 (2.46–33)	0.0001
Dyslipidemia	1 (2)	12 (23)*	12.6 (1.56–100)	0.0001

*Values that reached statistical significance

dyslipidemia and/or obesity, but not diabetes, were positively associated to the presence of NAFLD (Table 1).

Preoperative laboratory test values are shown in Table 2. As expected, group B subjects had significantly higher values of AST, ALT, ALP, and triglycerides. Preoperative ultrasonography accurately detected NAFLD in only seven patients (13%). In the multivariate logistic regression analysis, the following variables were considered: NAFLD, obesity, diabetes, dyslipidemia, gender, and hypertension. In this model, only obesity reached statistical significance (p=0.026). There were no complications or mortality secondary to the liver biopsies.

Discussion

GD and NAFLD share common risk and pathogenic factors. Obesity is a well-established risk factor for NAFLD and a major risk factor for developing gallstones.[14] The risk for GD is especially high if obesity onsets in youth. GD is closely related to central obesity, diabetes mellitus, and insulin resistance.[15–17] Other shared risk factors include dyslipidemia (hypertriglyceridemia, low HDL-C), abnormalities in fibrinolysis and coagulation.[18] NAFLD and GD appear to be linked through the metabolic syndrome, insulin resistance, and probably hyperhomocysteinemia.[9,19–23]

Fatty liver has been documented in up to 15% of healthy nonobese individuals and about 70% to 80% of obese individuals in some series. Fifteen percent to 20% of morbidly obese subjects have NASH and up to 20% of patients with NASH will develop liver cirrhosis over a period of 5 to 10 years.[24] In this study, we found that more than 50% of patients with GD have associated NAFLD. Subjects with GD and NAFLD had the typical risks factors for both diseases: older age, family history of hypertension, dyslipidemia and/or obesity, as well as higher body mass index and a higher prevalence of diabetes. The fact that

Table 2 Routine Laboratory Values

	Group A n=43	Group B n=52	p value
Glucose (mg/dL)	99.16±30.48	106.6±29.27	0.23
Cholesterol (mg/dL)	203.7±38.21	205.3±57.6	0.87
Triglycerides (mg/dL)	136.9±44.57	194.7±106.45*	0.007
HDL-C (mg/dL)	72.76±47.52	58±27.87	0.07
AST (U/L)	23.8±8.31	53.3±44.75*	0.0001
ALT (U/L)	28.6±8.34	58.3±35.69*	0.0001
ALP (U/L)	73.9±21.19	99±49.66*	0.0001
Total protein (g/dL)	7.49±0.57	6.8±0.49	0.93
Albumin(g/dL)	4.1±0.41	3.7±0.49	0.72
Hb_{A1c}	5.33±2.17	5.47±1.87	0.87

Data are expressed as the mean±SD
*Values that reached statistical significance

patients with NAFLD were significantly older than those with normal biopsies suggests that, given enough time, some of the latter patients may develop liver steatosis increasing the prevalence of NAFLD in patients with GD. It is important to remark that, in some liver and biliary diseases, genetic differences play a key role. Epidemiological studies, especially those of ethnic differences, family grouping, and twins, have suggested that genetic background is a risk factor for the development of gallstones.[25,26] Furthermore, it has been observed that Mexican–Americans have a correspondingly high prevalence and mortality from gallbladder cancer compared with non-Hispanic whites.[27–29] These studies suggest that abnormalities in genes related to the biliary secretion and/or liver function could be widely distributed in populations with Amerindian ancestry.

In our study, all subjects were Mexican Mestizo. Mestizo represents a complex mixture of European (Caucasian) and American native inhabitants (mongoloid) genetics and constitutes the core of Mexican and Latin American populations.[30] Thus, our study is just representative of our population. We believe that further studies that take ethnicity and genomic background into account are required to look for variables and genes that could be related to this association in other populations.

The vast majority of patients with NAFLD seek medical attention due to the incidental finding of elevated liver function tests during routine medical evaluations, assessment of unrelated symptoms, or metabolic syndrome. This apparent asymptomatic presentation does not imply a benign course. We found that only 13% of our subjects had a suspected diagnosis of NAFLD preoperatively. The rest of the patients were not aware of having any liver disease. NAFLD patients in our study had significantly higher values of AST, ALT, and ALP; nevertheless, as other series have confirmed, normal values do not exclude the diagnosis. A retrospective study by Mofrad et al. found that the entire histological spectrum of NAFLD can be seen in individuals with normal ALT values.[31] In most of our cases where abnormal liver function tests had been found in the preoperative evaluation, they were attributed to GD by the referring physician. Moreover, preoperative US was neither sensitive nor specific for the diagnosis of NAFLD. Our findings also support what other reports have suggested that imaging methods are of limited value as a screening method for NAFLD.

Previous studies have reported that almost 10% of patients with NAFLD have histological findings compatible with NASH or cirrhosis at the time of the diagnosis. In our series, almost 10% of GD with NAFLD had significant fibrosis. These findings underscore the clinical relevance of NAFLD and the importance of an early diagnosis in patients at risk. Awareness of the association between NAFLD and GD may result in an earlier diagnosis.

Liver biopsy is currently the only way to confirm a diagnosis of NAFLD and determine disease severity, yet there are no guidelines of when to perform a liver biopsy in patients at high risk of the disease.[32] Its relevance has been a matter of great controversy and an unattractive diagnostic option to many. Critics of liver biopsy argue that the quality of liver biopsy specimens is not always optimal and is subject to sampling variability.[33–35]Moreover, there is no agreement on which biopsy technique provides better material for analysis. Wedge biopsy has been criticized as a screening tool for being a subcapsular sample. Fibrous septa spreading from Glisson's capsule to the adjacent parenchyma may mimic cirrhosis, therefore, overestimating the stage of liver disease. One recent study found needle biopsies to be as effective as wedge biopsies in assessing the degree of steatosis in morbidly obese patients but that the presence of subcapsular fibrosis in needle biopsies was less than in wedge biopsies.[36] Older series report that both wedged and needle biopsy samples are appropriate for assessing the degree of fibrosis or cirrhosis.[37] Significant variability has been also observed between right and left lobe liver biopsies.[34]

Liver steatosis without NASH appears to be a frequent finding, and performing a liver biopsy in all suspected patients may appear overaggressive, especially when a treatment of proven benefit is lacking. Our study helps to understand the prevalence of asymptomatic liver disease in patients with symptomatic GD and to quantify the effect of certain risk factors.

In a population at increased risk of NAFLD, such as patients with symptomatic GD who undergo cholecystectomy, liver biopsy represents an opportunity to screen for the disease with minimal risk and cost to the patient. Laparoscopic liver biopsy in this group of patients is a safe and effective method to establish the diagnosis and stage of NAFLD and the information obtained could help to better understand the disease and its natural history. Additionally, it would give sufficient grounds to recommend at least the implementation of lifestyle modifications (diet, weight loss, exercise, cease of alcohol consumption) based on objective information. Severe histological findings may prompt participation of affected individuals in clinical trials of investigational drugs.

Although our finding that NAFLD is highly prevalent in subjects with GD may justify routine liver biopsy in all patients undergoing laparoscopic cholecystectomy, there are some limitations that should be acknowledged. As other reports have shown, there is significant interobserver and intraobserver variability in biopsy specimen interpretation.[38] Our specimens were reviewed by a single experienced pathologist and we believe that independent corroboration of the diagnosis and grade by another pathologist would strengthen our results. Another limitation in the design of the study is that a diagnosis of diabetes

rather than insulin resistance was used; hence, it is likely that some patients could have undiagnosed diabetes. We also acknowledge that the alcohol intake cutoff value of 150 g/week used in our study is higher than that used in other series. Nevertheless, there is no universally accepted threshold level of alcohol intake to distinguish alcoholic fatty liver disease from NAFLD and it is generally accepted that fatty liver does not develop with alcohol consumption levels below 20 g/day. Moreover, quantification of alcohol intake is largely subjective and has been known to be notoriously inaccurate in spite of using standardized instruments.

In conclusion, our findings suggest that routine liver biopsy during cholecystectomy for GD may be justified given the high prevalence of NAFLD in these patients which otherwise could go unrecognized for several years. Based on our results, obese and/or dyslipidemic patients with abnormal liver chemistry represent a group which would benefit the most by this approach. The information obtained by this practice could help to better understand the pathogenesis of NAFLD, lower its impact, and prevent or delay its complications. Even though there were no complications in our series, some complications are eventually inevitable and, therefore, the adoption of a practice of routine liver biopsy during laparoscopic cholecystectomy should not be based on the results of a single study. Further studies are needed to assess the feasibility, safety, efficacy, and cost-effectiveness of this approach in order to recommend it as a screening tool in this population.

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Discussion

Michael G. Sarr, M.D. (Rochester, MN): I have three questions. First, this is in a Mexican population, and so how representative of the rest of the genomic world is it? Second, if you find somebody with fatty liver disease, how are you going to treat them? I don't know of many effective therapies for NAFLD. And third, can you select out the patients whom you should biopsy? So if they are skinny and they don't have any other of these risk factors, do you need to biopsy them as well?

Jose M. Remes-Troche, M.D. (Veracruz, Mexico): Thank you for your questions. The first question, I think it is very important to remark that in many liver and gallstones diseases, ethnicity has a key role. There are several studies that have shown that gallstone disease is more prevalent in some Latin American countries and in some populations like Hispanics and Native American Indians. Thus, our study is just representative of our population. We believe that further studies regarding ethnicity and genomic issues are required, trying to look for which genes could be related to predicting and try to see if this is the same phenomenon in other populations.

Regarding the second question, one of the main problems that actually we have as a physician is the lack of a gold standard treatment for NAFLD. However, several recent studies have shown that in NAFLD, morbidity and mortality related to liver disease, but mainly to coronary artery disease, is considerably higher. So even if we don't have good medical treatment, we believe that reinforcement of changes in lifestyle, such as exercise and weight loss, are extremely important in these patients. It was surprising for us that three patients without any other apparent risk factors for fibrosis were diagnosed with early stage liver cirrhosis. This observation is very important because, besides the gallstones disease, the patients were consider as otherwise "healthy" subjects.

And regarding your third question?

Dr. Sarr: Can you select out the patients whom you should biopsy?

Dr. Remes-Troche: Yes. One of the messages of this study is that patients with gallstones diseases and NAFLD have some preoperative risks factors associated such as dyslipidemia, diabetes, and obesity. Thus, at least in our population, recognition of these risk factors could help to select patients. Also, this information is useful to let know patients the importance of take a liver biopsy during the cholecystectomy.

J Gastrointest Surg (2008) 12:2103–2109
DOI 10.1007/s11605-008-0706-5

Single-blinded Randomized Trial of Mechanical Bowel Preparation for Colon Surgery with Primary Intraperitoneal Anastomosis

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Received: 14 May 2008 / Accepted: 8 September 2008 / Published online: 27 September 2008

Abstract

Introduction We report the final analysis of a prospective single-blinded randomized trial designed to investigate whether omission of preoperative mechanical bowel preparation increases the rate of surgical-site infection and anastomotic failure after elective colon surgery with intraperitoneal anastomosis by a single surgeon.

Patients and Methods Patients scheduled to undergo an elective colon or proximal rectal resection with a primary anastomosis by a single surgeon were randomized to receive either oral polyethylene glycol (Group A) or no mechanical bowel preparation (Group B). Patients were followed by an independent surgeon.

Results One hundred and forty nine patients were enrolled. Three patients (2%) were preoperatively excluded because of active immunosuppression and 13 (9%) were excluded from the final analysis. Of the remaining 129 patients, 65 were assigned to Group A and 64 to Group B. Thirty patients (23.2%) developed wound infection, (Group A=24.6% and Group B=17.2%; NS). There were three cases of intra-abdominal sepsis a (Group A 4.6%). The anastomotic failure rate was 5.4% (n=7), four patients in Group A (6.2%) vs. three patients in Group B (4.7%) (NS). When SSI and anastomotic failure were combined, the complication rate in Group A was 35.4% vs. 21.9% for Group B. The NNH was 7.4.

Conclusion Our final analysis shows that a single surgeon will not have a higher rate of either surgical-site infection or anastomotic failure if he/she routinely omits preoperative mechanical bowel preparation.

Keywords Colon · Surgery · Mechanical bowel preparation · Randomized trial · Single-blinded · Complications

Introduction

For many years, mechanical bowel preparation (MBP) for elective colorectal surgery has been a surgical "dogma" beyond criticism.[1–4] The rationale for the use of MBP was to decrease peritoneal contamination during the procedure. However, an increasing number of randomized trials and meta-analysis have consistently shown that this practice is unnecessary[5–11] or even associated with deleterious effects.[12–15]

Following recommendations by experts and guidelines, MBP was a standard practice at our Department for decades, but we were puzzled by the contradiction between the standard of care and the scientific evidence published in the literature. As suggested by Bucher et al.,[16] it is difficult to trust results from flawed trials and most of them have a skewed balance between their sample size and their control of experimental conditions. Therefore, we designed a prospective single-blinded randomized trial to investigate whether omission of preoperative mechanical bowel preparation increases the rate of surgical-site infection and anastomotic failure after elective colorectal surgery performed by the same surgeon. An interim analysis was previously published.[17] This is the report of the final analysis.

This work was presented in abstract form at the 50th Meeting of the Society of Surgery of The Alimentary Tract.

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Patients and Methods

Design and Statistical Analysis

This is a single-blinded randomized trial based upon the fact that MBP was the standard of care for prevention of septic complications after elective colon surgery.[18] After reviewing historical data from our Department, we found that our expected wound infection rate for these operations with routine MBP was about 10% for clean-contaminated procedures and about 30% for dirty surgery (unpublished data). Thus, we considered that it would be clinically relevant for an individual surgeon if, by omitting MBP, his/her SSI rate (incisional+organ/space) would triple. In other words, omission of MBP would convert elective colorectal surgery from a clean-contaminated into a dirty procedure.

The primary end-point was surgical-site infection (SSI) and the secondary was anastomotic leakage. A sample size of 62 patients for each arm was calculated to detect an increase in the SSI rate from 10% to 30% with an α error of 0.05 and a power of 80% for a two-tailed comparison. Data were entered into a computerized database and analyzed with the SPSS software package. The number-needed-to-treat or harm (NNT or NNH) was calculated as the inverse of the increase in relative risk. Student's *t*, Pearson's Chi square, and Fisher exact tests were used for statistical analysis as indicated. Statistical significance was defined as $p<0.05$.

The trial was approved by the ethics committee of Hospital Clinico San Carlos.

Study Participants

From October 2001 to January 2007, all patients scheduled to undergo an elective colorectal procedure with a primary intraperitoneal anastomosis without intraoperative colonoscopy and to be operated on by the same surgeon were included in the study if they: (1) had not had an endoscopic exploration in the prior week, (2) were 18 years of age or older, and (3) had given informed consent. Patients enrolled in the study were subsequently admitted and randomized by computer-generated numbers to receive either 3 l of polyethylene glycol lavage solution orally plus conventional enemas (Group A) over 24 h or to have no mechanical bowel preparation whatsoever (Group B) prior to surgery. The primary surgeon was blinded to the randomization process and the preparation status of every patient. The criteria for exclusion from the analysis after randomization were active immunosuppression (including poorly controlled conditions that could increase the infection risk, such as diabetes mellitus, HIV infection, etc.), preoperative chemoradiation, diverting stoma, and perforated or obstructed tumor.

Procedures

Patients randomized to Group A received a liquid diet for 24 h prior to the procedure, whereas in Group B, patients were on a regular diet until the night before surgery. Oral intake cessation was ordered 9–12 h before the operation. No intravenous fluids were administered as a part of the preoperative protocol. Patients' compliance with the cleansing protocol was supervised and assessed by a registered nurse. Antibiotic prophylaxis consisted of intravenous administration of gentamicin and metronidazole (80 mg and 500 mg, respectively), 30 min before incising the skin and every 8 h postoperatively (three doses). Anti-thrombotic prophylaxis was based on preoperative and postoperative administration of subcutaneous low molecular weight heparin (enoxaparin 40 mg or 60 mg depending on individual risk factors). The approach to the abdominal cavity was standardized as previously described.[17] Both ends of the intestinal segment were sectioned with staplers (GIA, Tyco Healthcare) to avoid the spillage of feces. Anastomoses were hand-sewn or stapled according to the preference of the surgeon. No additional irrigation with antibiotic or antibacterial solutions was used during the operation. Intra-abdominal drains were never used after the primary procedure and skin incisions were always closed with staples. Peritoneal contamination during the procedure was prospectively assessed, although it was not specifically studied for the interim analysis, using an arbitrary scale: Grade 0—minimal amount of feces in any of the bowel stumps after removing the staples, which were easily cleansed with a gauze or by gentle suction; no spill; Grade I—feces in any of the stumps after removing the staples, that required repeated cleansing with gauzes or intense suction, and/or minimal contamination of the adjacent peritoneum with bowel content; Grade II—uncontrolled spillage of feces.

Patients were followed for SSI (wound infection+intra-abdominal sepsis) and anastomotic failure within 30 days (with weekly visits to our outpatient clinic) after surgery by a trained surgeon who was not involved in the study and had no information on patients' preparation status. SSI was diagnosed and classified following the definitions made in the 1999 CDC guidelines[18] as superficial incisional SSI, deep incisional SSI, and organ/space SSI. Anastomotic failure was diagnosed if there was a fecal fistula, an anastomotic dehiscence was identified at re-operation or during post mortem, and/or if clinical suspicion was confirmed by a radiological test (computerized tomography).

Results

Up to January 2007, one hundred and forty five patients who met the inclusion criteria had been enrolled in the study. The trial profile is depicted in Fig. 1. Three patients

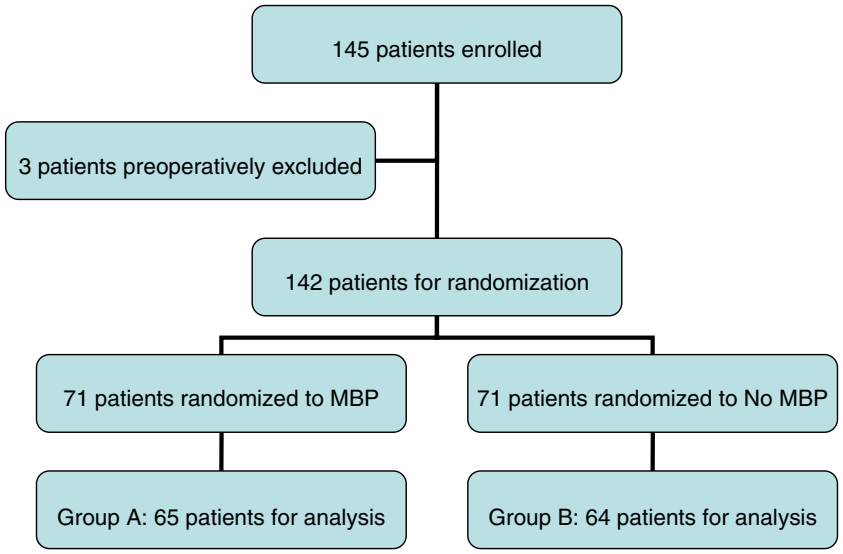

Fig. 1 Study profile. Patients on active immunosuppression (including patients with poorly controlled immunosuppressive conditions) or preoperative chemoradiotherapy were excluded from the study before randomization.

(2%) were excluded before randomization because they were on active immunosuppressive therapy for severe connective tissue disorders. Subsequently, one hundred and forty two patients were randomly assigned to one of the two arms, but 13 of them (9%) were excluded from this final analysis because they met at least one of the exclusion criteria (diverting stoma in ten cases, contained perforation in one patient and unresectable tumor in two patients). Of the remaining 129 patients left for the analysis (89%), 65 had been included in Group A and 64 in Group B. No significant differences in demographics were found between groups, as presented in Table 1. Antibiotic and anti-thrombotic prophylaxis were systematically used. No discontinuation of the cleansing protocol was needed in Group A and no patient was lost to follow-up. Contamination of the abdominal cavity during the procedure was not an issue for the surgeon, irrespective of whether patients were submitted to MBP or not (Table 2).

As shown in Table 3, surgical-site infection occurred in 30 of the 129 patients included in the study (23.2%), with superficial incisional SSI being the most frequent presentation (Group A=24.6% and Group B=17.2%; NS). There were three organ/space surgical-site infections, but all of them occurred in Group A. Thus, although SSI was more frequent in patients receiving mechanical bowel preparation (29.2% vs.17.2%), no statistically significant difference between groups was detected.

No statistically significant difference in the intestinal segments involved in the anastomosis was observed. Specifically, ileorectal anastomosis were carried out in three patients (4.6%) in Group A and one patient (1.6%) in Group B, whereas colorectal anastomosis were performed in 28 patients (43.1%) in Group A and 24 patients (37.5%) in Group B. The results related to the secondary end-point are presented in Table 4. The overall rate of anastomotic failure was 5.4% (n=7), 6.2% of patients in Group A (n=4) and 4.7% in Group B (n=3). As we previously reported, it

Table 1 Preoperative Demographics

	Overall (n=129)	Group A (n=65)	Group B (n=64)	p
Age (years)	67.2±14	67.2±13	67.4±16	NS
Sex (F/M)	61/68	29/35	32/33	NS
IBD	8 (6.2%)	3 (4.6%)	5 (7.8%)	NS
CRC	101 (78.3)	50 (77%)	51 (80%)	NS
Other	20 (15.5%)	12 (18.5%)	8 (12.5%)	NS
AB	100%	100%	100%	NS
Enoxaparin	100%	100%	100%	NS
Anastomosis				
SB–LB	63 (48.9%)	29(22.5%)	34(26.4%)	NS
LB–LB	66 (51.2%)	36(27.9%)	30(23.3%)	NS
Hand-sewn	76 (58.9%)	35(27.1%)	41(31.8%)	NS
Stapled	53 (41.1%)	30(23.3%)	23(17.8%)	NS

Indication for surgery and procedure-related data
IBD Inflammatory bowel disease, *CRC* colorectal cancer, *AB* antibiotic prophylaxis, *SB* small bowel, *LB* large bowel

Table 2 Contamination of the Peritoneal Cavity as Assessed by the Surgeon

	Group A (n=65)	Group B (n=64)	p
Grade 0	61 (93.8%)	62 (96.9%)	NS
Grade I	4 (6.2%)	2 (3.1%)	NS
Grade II	0	0	

was higher in those cases in which two segments of the large bowel were involved in the anastomosis, compared to the anastomosis between the small and large bowels (7.6% vs. 3.2%), but it did not reach statistical significance.

If the frequency of SSI and anastomotic failure, which are the aim for the preventive use of MBP, are added the complication rate in Group A was 35.4% (23 of 65) vs. 21.9% (14 of 64) for Group B, but again the difference was not statistically significant for this sample size. The absolute risk reduction obtained by omitting MBP was 13.51% [95% CI −1.91, 28.93%] and the number-needed-to-treat was 7.4, that is, when MPB is omitted in 7.4 patients, one complication is prevented.

Seven patients (5.4%), with a mean age of 81.0±7 years, died within 30 days of the operation, three in Group A and four in Group B, with similar mortality rates in both groups (4.6% in Group A vs. 6.3% in Group B; NS). All deaths occurred in patients older than 80 years (six of 11) or with advanced disease (one of seven). In only three cases, a direct relationship with a previous anastomotic dehiscence was found (one patient in Group A and two patients in Group B). One of those patients, who recovered after re-operation, and the remaining deaths (n=4) occurred as a result of cardiovascular events.

Discussion

Surgery is a complex scenario to generate hard and reproducible scientific evidence that surgeons could easily translate into clinical practice. It is almost impossible to design the perfect surgical randomized trial because there is an unsolvable conflict between a strict control of technical variability and a large sample size. Frequently, larger number of patients are recruited (many different surgeons with different trainings and from multiple institutions do few cases) to decrease the impact of variations in practice.[20, 21] However, we chose to question the "surgical dogma" for elective colon surgery by doing just the opposite, that is, to investigate if a single surgeon would have poorer outcomes after omitting MBP, while maintaining a tight control over experimental conditions. In our previously published interim analysis ([17]), anastomotic failure was more frequent in patients who had MBP (p=0.05) and although the infection rate was also greater in that group of patients, the difference did not achieve statistical significance. This was consistent with what had been found in other randomized trials and meta-analysis ([5–16, 20–22]). Now, our final results of a single-blinded prospective randomized trial show that a surgeon who adheres to the "surgical heresy" of avoiding preoperative MBP for elective colon procedures with intraperitoneal anastomosis will not get the high infection rates expected for dirty surgery. However, the trend towards poorer results with colonic cleansing in terms anastomotic failure, that was suggested in the interim analysis, has not been confirmed.

The rationale for MBP in elective colon procedures is to reduce the contamination of the surgical field, subsequently decreasing the risk of infection and preventing anastomotic failure. In agreement with previous trials, no statistically significant difference in the risk of SSI was found between groups in our study. It can be argued that our wound infection rate is rather high in patients with MBP, which would bias our results and invalidate any conclusion. Certainly, most randomized trials have reported SSI rates about 10%,[5–11] whereas we had incisional SSI rates of 24.6% and 17.2% in patients with and without MBP, respectively. However, our wound infection rates are only slightly higher than those recently reported by Contant et al. in a multi-center study.[19] We believe that, in general, postoperative wound infection is underreported in colorectal surgery trials due to methodological issues (diagnostic criteria, biased assessment, and differences in follow-up). For example, Smith et al.[20] hypothesized that incisional

Table 3 Results Related to the Primary End-point

	Overall (n=129)	Group A (n=65)	Group B (n=64)	p
Incisional SSI	27 (20.9%)	16 (24.6%)	11 (17.2%)	NS
Organ/space SSI	3 (2.3%)	3 (4.6%)	0	NS
Total SSI	30 (23.2%)	19 (29.2%)	11 (17.2%)	NS

SSI Surgical-site infection

Table 4 Anastomotic Dehiscence Rate by Group and Intestinal Segment Involved in the Anastomosis

Anastomosis	Overall	Group A	Group B	p
SB–LB	2/63 (3.2%)	2/29 (6.9%)	0/34	NS
Ileocolostomy	1	1/26	0/33	
Ileorectostomy	1	1/3	0/1	
LB–LB	5/66 (7.6%)	2/36 (5.6%)	3/30 (10%)	NS
Colocolostomy	2/14	1/ 8	1/6	
Colorectostomy	3/52	1/28	2/24	
Total	7/129 (5.4%)	4/65 (6.2%)	3/64 (4.7%)	NS

SB Small bowel, *LB* large bowel

SSIs following elective colorectal resection were more frequent than generally reported in the literature and, in a retrospective study, found that the postoperative infection rate by a single surgeon—using MBP—was 26%, exactly the same as ours.[20] Furthermore, Wick et al. have reported a retrospective study showing that their postoperative infection rate for colon surgery is 20% and concluded that "… The rate of surgical-site infection after colorectal surgery is likely to be higher than that reported in national quality improvement programs".[23]

In our interim analysis of the secondary end-point, we reported an increased risk of anastomotic failure in the MBP group that almost reached statistical significance ($p=0.05$). In this final analysis, there was still a higher incidence of leaks when MBP was used, but even though the sample size is larger, it is not statistically significant ($p=0.5$). The two largest and most recently published multi-center randomized trials showed no differences in anastomotic leaks.[19, 21] although they were more frequent in patients without MBP. In contrast, a meta-analysis has shown that MBP increases the risk of anastomotic failure,[22] with figures comparable to ours (5.1% vs. 2.6%), although it includes patients with intraperitoneal and extraperitoneal anastomoses with protective ostomies.

One of the major limitations that can be argued against our study is its sample size. Yet, the strength of the design, compared to majority of larger trials and meta-analysis addressing MBP, is due to the fact that the primary surgeon and those following patients and reporting the complications were blinded to their preparation status. In addition, we only included patients with intraperitoneal anastomosis, without diverting stomas or immunosuppressive therapies in order to reduce additional risks of infection beyond our control. Obviously, these restrictions prolonged the duration of the study and limited its sample size but gave us a tighter control over the experimental conditions (surgical technique, fewer confounding variables for infection and dehiscence, and postoperative management).

Clinically speaking, the most relevant question that arises after conducting an investigation like this is "Will you change your practice?" Taking into account the patient's perspective, as reported by Jung et al.,[24] the outcomes of MBP published in meta-analysis and our own results, we have abandoned the routine use of colonic cleansing for elective open colonic surgery if intraoperative colonoscopic exploration is unnecessary. However, this study cannot elucidate the role of MBP in patients undergoing laparoscopic surgery. Therefore, specific studies should be carried out to address that important issue.

In conclusion, our final analysis of a prospective single-blinded randomized trial of mechanical bowel preparation shows that a surgeon, who performs about 30 colon resections with intraperitoneal anastomosis per year, will not get higher surgical-site infection rates if he/she routinely omits preoperative mechanical bowel preparation with polyethyleneglycol and conventional enemas. In addition, this practice will not result in a higher risk of anastomotic failure or postoperative mortality. Therefore, irrespective of the intrinsic and absolute value of mechanical bowel preparation, patients undergoing elective colon surgery by an individual surgeon would not benefit from having preoperative colonic cleansing.

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Discussion

Final Analysis of a Single-Blinded Randomized Trial of Mechanical Bowel Preparation for Elective Colon Surgery with Primary Intraperitoneal Anastomosis by a Single Surgeon

Madhu Prasad, M.D. (Detroit, MI): I would like to congratulate you on a very fine presentation and also thank you for kindly providing me an early iteration of your manuscript prior to the meeting.

A study like yours a generation ago would have been considered heretical, but there are more and more reports in the literature similar to yours. Despite that, I think in the United States, as you pointed out in your presentation, the notion of elective operation on the colon absent mechanical bowel preparation is something with which many are uncomfortable. As you know, I do not do many colonic procedures, though it is very clear that most of my patients do not listen to my instructions and they come unprepped to surgery anyway. But let me ask you a couple of questions.

Firstly, most of the studies like this that I have seen in the literature tend to be multi-center and multi-surgeon trials. So tell me a little bit about why a single-blinded and single-surgeon study design such as you employed enabled you to make more discrete conclusions? Secondly, have you tried this in the laparoscopic setting, and if not, do you think that there is any application of this in the laparoscopic setting? Thirdly, why did you choose to restrict your analysis to intraperitoneal anastomoses and exclude rectal tumors altogether?

I noticed in your last couple of slides that the rate of surgical-site infection you report in patients who underwent mechanical bowel preparation was 24.6%, which is roughly two- or three-fold higher than reported in most papers in the literature for clean-contaminated surgery. Could you speculate as to the reasons for this, and do you think that this number might have skewed your conclusions in favor of foregoing mechanical bowel preparation?

And finally, do you find that patients that do not undergo mechanical bowel prep require less fluid in the perioperative period and does that enable you to fast track these patients?

Julio M. Mayol, M.D. (Madrid, Spain): Thank you very much, Dr. Prasad. First of all, we designed a single-blinded trial because we wanted to control the experimental conditions of our study as much as possible. When surgeons evaluate their own results, they are usually biased, and we wanted to avoid that. At the same time, we were trying to control for technical variability. Multi-center and multi-surgeon trials are criticized because they disregard technical variability. So by conducting a single-blinded trial with a single surgeon, we obtained a tighter control over our experimental conditions.

Secondly, yes, we have done some cases without mechanical bowel preparation laparoscopically, but with this trial, we cannot answer your question. We would need specific randomized trials to study the impact of mechanical bowel preparation on laparoscopic cases.

With regard to the reason why we just restricted the study to intraperitoneal anastomoses, again, the answer is that we wanted to control the confounding variables. If we had included pelvic anastomoses, most of those cases would have undergone preoperative chemoradiotherapy and had a diverting stoma. Therefore, several additional confounding variables would have been included, making it difficult to interpret their effects on the results and neglecting the advantage of a strict design. That is why we restricted the patients to those who had an intraperitoneal anastomosis.

Four is our infection rate. It is rather high, and we were surprised. But in our study, the surgeon who operated on the

patient was not the one reporting the complications. They were assessed by an independent observer; and we were puzzled by the high infection rate, of course. So we went back to the literature. And in 2004, Smith published a retrospective study in the Annals of Surgery showing that when patients are specifically followed up, the infection rate for colon surgery carried out by single surgeon using mechanical bowel preparation was 26% in the United States. So probably in most single trials, where observers are not blinded, there are biases in reporting complications.

And finally, the fast track. Our anesthesiologists complained when patients had had mechanical bowel preparation in the past about the amount of fluid that they need intraoperatively. Older and sick patients suffer from electrolyte imbalance and get dehydrated. They usually need very strong supportive therapy both intraoperatively and postoperatively, and that probably impairs the recovery of those patients. It would be counterintuitive to fast track patients who have mechanical bowel preparation.

Richard A. Hodin, M.D. (Boston, MA):

A quick question on the resolution of ileus. I do not know how carefully you looked at this, but I wonder whether there was any difference in the two groups in terms of passage of gas, bowel movements, and so forth?

Dr. Mayol: We did not look specifically at that, but there are data in the literature from multi-center trials showing that by avoiding mechanical bowel preparation, a shorter postoperative ileus duration is achieved, although it is just 1 day. Patients without mechanical bowel preparation pass gas 1 day before than those who had it. And oral intake is resumed 1 day before. But, again, we did not look at that specifically.

J Gastrointest Surg (2008) 12:2110–2118
DOI 10.1007/s11605-008-0714-5

Factors Related to Anastomotic Dehiscence and Mortality After Terminal Stomal Closure in the Management of Patients with Severe Secondary Peritonitis

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Received: 19 May 2008 / Accepted: 18 September 2008 / Published online: 16 October 2008

Abstract
Introduction Management of severe secondary peritonitis (SSP) may require intestinal resections and bowel exteriorization due to an unacceptable high risk for anastomotic dehiscence (AD). Bowel exteriorization can be achieved through loop or terminal stomas. There are no studies addressing the fate of these latter. Our aim was to determine factors associated with AD and mortality in patients submitted to restoration of intestinal continuity after creation of terminal stomas as part of their operative management for SSP.
Patients and Methods We analyzed prospectively collected databases on all consecutive patients with SSP submitted to restoration of intestinal continuity after having had terminal ileostomies (TI) or terminal colostomies (TC) as part of their operative management during a 30-month period. Several patient and disease and operative variables were evaluated as factors related to AD and mortality in this group of patients. Univariate statistical comparisons were made using Student's *t* test for continuous variables and chi-square test when categorical variables were compared. Multivariate analyses were also performed.
Results A total of 72 male patients and 36 female patients were included in the study; 54 had TI and 54 had TC. Median number of operations performed as part of their management for SSP (prior to stomal closure) was 2 (range, 1–15). A total of 76 (70%) had had diffuse peritonitis, and 39 (36%) required management with an open abdomen (26 of them with a skin-only closure technique). Median time interval between stomal creation and closure was 190 days (range, 14–2,192). Stapled and hand-sewn anastomoses were done in 24 and 84 patients, respectively. AD occurred in 11 patients (10%). Univariate analyses disclosed age ≥50 years ($p<0.05$), high American Society of Anesthesiologists (ASA) score (≥3; $p<0.01$), history of chronic renal failure ($p<0.04$), history of diffuse peritonitis ($p<0.05$), management with an open abdomen ($p<0.05$), and lower preoperative hemoglobin values ($p<0.05$) as risk factors for AD. Only age ≥50 years prevailed after multivariate analyses. A total of seven patients died (6%). Factors associated with mortality were age ≥65 years ($p<0.02$), high ASA score (≥3; $p<0.01$), preoperative use of total parenteral nutrition ($p<0.02$), lower preoperative hemoglobin values ($p<0.05$), time interval between stomal creation and closure <3 months ($p<0.01$), AD ($p<0.02$), and need for reoperation after stomal closure ($p<0.02$). After multivariate analyses, time interval between stomal creation and closure <3 months and need for reoperation were the only ones that prevailed as independent risk factors for mortality ($p<0.05$).
Conclusions Although several variables were related to AD and mortality, waiting at least >3 months before attempting restoration of intestinal continuity seems to be the best approach and a practical recommendation in this group of challenging patients.

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Keywords Terminal ostomies · Stomal closure · Severe secondary peritonitis · Anastomotic dehiscence · Source control · Surgical complications

Introduction

Source control is the initial and most important step in the operative management of severe secondary peritonitis (SSP).[1] Some patients may require resection of affected bowel in order to eliminate the focus of infection. Once resected, surgeons are faced with a dilemma over whether to anastomose (with or without a *protective* loop ostomy), exteriorize the proximal bowel end with closure of the distal end, or exteriorize both bowel ends. In reaching a decision, various factors must be assessed, which among others include, extent of intraabdominal (IA) contamination, source of infection, and patient's functional status and premorbid reserve.[2]

When difficult IA sepsis and SSP is being managed, resection and exteriorization seems to be the safest choice, since it may be technically easier and quicker, and it avoids further risks of anastomotic breakdown and on-going, life-threatening peritoneal contamination. Moreover, some patients will need multiple planned or "on demand" relaparotomies and may even require an open-abdomen management to ease new re-entrees into the abdomen and/or to avoid development of the abdominal compartment syndrome.[3] Suture lines under these conditions would be further put under undue risks.

Some patients will die during management for SSP (~40% to 80%)[3]; for those survivors who were submitted to an ileostomy or colostomy as part of their operative management, new operations will be needed in order to restore intestinal continuity. Reported herein is our experience with a group of consecutive patients with SSP who were submitted to terminal ileostomy (TI) or terminal colostomy (TC) during the course of their operative treatment. They were then reoperated in an elective fashion to achieve ostomy reversal. Our aim was to determine factors related to anastomotic dehiscence (AD) and mortality for this latter reoperation in this group of severely ill, multioperated patients.

Patients and Methods

During a 30-month period (March 2005–August 2007), we prospectively collected data of all consecutive patients that had been submitted to restoration of intestinal continuity in an elective fashion, after having had construction of a TI or TC as part of a source control procedure under emergency circumstances during management for SSP. Patients with proximal small bowel ostomies (jejunostomies) were specifically not included, as this group of patients require a different management algorithm. Moreover, because of their different nature, prognosis, and potential for reversal, patients with loop ileostomies or loop colostomies were also not included in this study. A total of 82 patients (76%) were referred from other centers where initial management for SSP had been started. Some even had their TI or TC already constructed. The other 26 patients (24%) were managed at our hospital since the beginning of illness.

Data Collection

Our data bases included demographics, presence of comorbidities, history of use of steroids, initial pathology leading to SSP, type of peritonitis (local or diffuse), number and type of operations performed for management of SSP, need for an open-abdomen management, interval (days) between TI or TC creation, and ostomy reversal. Prior to this latter, preoperative exams were performed in all patients; emphasis was placed on hemoglobin level, lymphocyte count, serum albumin, and total serum proteins. Need and duration for total parenteral nutrition (TPN) support prior to ostomy reversal was also documented. Operative data included ostomy location (ileum or colon), presence and number of inadvertent perforations and their management (i.e., primary closure, additional bowel resections, anastomosis, etc.), type of anastomosis performed for ostomy closure (hand-sewn or mechanical), operative blood loss, and need for blood transfusions. If reoperative treatment (after ostomy reversal) was undertaken, indications, timing (postoperative day), and type of reoperations were also recorded. Postoperative stay (calculated from stomal closure until discharge or death of the patient), presence of AD, and operative mortality (and its cause) were also documented. All patients were followed until hospital discharge or death.

Definition of Variables

Dependent variables were (a) AD, defined as leakage of luminal contents from the surgical join done for ostomy reversal,[4] and diagnosed clinically, through imaging (contrast) studies and/or operatively; and (b) operative mortality, defined as death occurring during postoperative hospitalization or during the first 30 postoperative days in those patients that were discharged from the hospital. Our aim was to determine risk factors that were associated to them. These factors (independent variables) included age (divided by lustrum), gender (male/female), presence of comorbidities (according to the Elixhauser index), location of the perforation (ileum, appendix, or colon), American Society of Anesthesiologists (ASA) score, site where primary surgery was performed (transfer or at our institution) number of operations required for management of SSP, type of peritonitis (local, one IA quadrant vs diffuse, ≥2 IA quadrants), need for an open-abdomen management, need for preoperative TPN support, biochemical parameters (hemoglobin (grams per deciliter), total lymphocytes (total per cubic millimeter), serum albumin

(grams per deciliter), total serum proteins (grams per deciliter), and interval (days) between TI or TC creation and ostomy reversal, intraoperative blood loss (in milliliters), intraoperative red blood cell transfusion (yes or no), and type of anastomosis (hand-sewn vs stapled).

Statistical Analysis

All data were collected and entered in a computerized Microsoft Excel database (Microsoft, Redmond, WA, USA). Analyses were performed with the statistical package program SPSS version 14 (SPSS, Chicago, IL, USA). Unless specified otherwise, numerical values are expressed as median (and range). To determine factors associated to AD and mortality, Student's t test was used to perform comparisons between continuous variables and Pearson chi-square test for categorical variables. All comparisons are two-tailed probabilities. Significance was determined at the 95% confidence interval (95% CI, $p \leq 0.05$). To determine independent risk factors, significant variables found through univariate analyses were then submitted to multivariate analyses (logistic regression). Odds ratios were calculated for these factors.

Results

A total of 108 patients were included: 72 males (67%) and 36 females (33%), with a median age of 55 years (range 20–86). Fifty-four (50%) had TI, and 54 (50%) had TC. Comorbidities were found in 39 patients (36%); these included high blood pressure ($n=35$), diabetes mellitus ($n=10$), ischemic cardiopathy ($n=7$), and chronic renal failure ($n=3$). Only two patients reported use of steroids.

After treatment for SSP was successfully accomplished, most patients were discharged and followed up on an ambulatory basis until reoperation for ostomy closure was deemed feasible. Eleven patients never left the hospital between management for SSP and ostomy closure; nine of them required TPN, and the other two had local peritonitis, and their stomas were closed "early" 14 and 19 days after their construction with no further morbidity.

Besides the nine patients requiring TPN during the same hospitalization, two others used it after being discharged and readmitted for ostomy reversal; thus, in total, 11 patients (10%) utilized TPN for a median of 32 days (range, 14–100). They all had in common a high output of their TI.

Management of SSP

During the course of their disease, 76 patients (70%) had diffuse peritonitis, and 39 (36%) required management with an open abdomen (26 of them with a skin-only closure technique and 13 with the "Bogota Bag"). Table 1 depicts the complete list of pathologies that led to SSP and their relationship with presence of diffuse peritonitis and/or need for open-abdomen management.

Median number of operations performed during management of SSP was 2 (range 1–15). Table 2 lists all operations where TI and TC were created. Interestingly, the number of operations for source control was significantly higher for patients managed with an open abdomen (mean and (SD) of 3.28 (±3.19) vs 1.52 (±0.68), ($p<0.001$)).

TI and TC were performed during the first, second, third, and fourth operations for SSP in 63, 33, nine, and three patients, respectively; source control was achieved through bowel exteriorization in 48 of 63 (76%), 22 of 33 (67%), eight of nine (89%), and three of three (100%) in that same sequence of operations. Thus, once TI and TC were successfully fashioned, source control was achieved in a total of 81 patients (75%) who did not need any more operations and awaited for stomal closure. The other 27 patients (25%) required a total of 52 further surgical procedures, which included IA lavages ($n=36$), stomal

Table 1 Initial Pathologies Leading to SSP and Its Relationship with Diffuse Peritonitis and Need for Open-Abdomen Management

Initial pathology	Samples	Diffuse peritonitis	Open abdomen
Complicated diverticular disease	43	29	12
Complicated appendicitis	19	15	8
Complicated intestinal obstruction	11	9	6
Small bowel perforation	11	6	3
Iatrogenic small bowel perforation (gynecological procedure)	7	6	3
Trauma	5	3	2
Ischemic colitis	4	3	2
Others[a]	8	5	3

SSP severe secondary peritonitis

[a] Others: anastomotic dehiscence after colostomy closure (two), small bowel perforation post-nephrectomy (two), cholecystectomy (one), colonoscopic colonic perforation (one), sigmoid volvulus (one), and anastomotic dehiscence (ileal tumor)

Table 2 List of Operations During which the Bowel Was Exteriorized and the Stoma Created

Operation	Samples
Sigmoidectomy	32
Right hemicolectomy	24
Small bowel resection	23
Left hemicolectomy	8
Relaparotomy for AD after (previous) colostomy closure	6
Small bowel resection (after gynecologic operation)	5
Transverse colon resection	3
Relaparotomy for AD after (previous) ileostomy closure	2
Subtotal colectomy	2
Other colonic resections	2
Colonic resection (after gynecologic operation)	1

AD anastomotic dehiscence

reconstructions (n=8), fascial closures (n=4), management of intestinal obstruction (n=2), and others.

Operative Data (Stomal Closure)

Fifty-four patients (50%) had TI, and 54 (50%) had TC. All stomal closures were performed at our hospital.

Median interval (days) between stomal creation and closure was 190 days (range, 14–2,192). By comparing this interval according to stomal location (ileal vs colonic), no significant difference was found. A marked trend toward a longer waiting period, however, was found in patients with more operations for source control (269 vs 184 days), history of diffuse peritonitis (205 vs 160 days), and need for an open-abdomen management (220 vs 183 days); none of these differences were statistically significant. Mean (SD) and median postoperative stay (days) was 25.12 (±53.33) and 9 (range 3–312), respectively.

During dissection, there were incidental enterotomies in 15 patients (14%); management included primary closure in nine, resection and anastomosis in two, and in the remaining four patients, enterotomies were included in the segment of bowel to be resected for stomal closure, and thus, no other anastomosis or primary closure were required. No significant differences were observed in the incidence of these types of lesions and number of operations performed for SSP, history of diffuse peritonitis, need for an open-abdomen management, and interval between ostomy creation and closure.

For ostomy reversal, stapled and hand-sewn anastomoses were done in 24 (22%) and 84 (78%) patients, respectively. Median intraoperative blood loss was 200 ml (range, 50–1,500); four patients required intraoperative blood transfusions.

A total of 28 reoperations were required in 18 patients (17%); five of them needed >1 relaparotomy. Indications for initial re-explorations included postoperative intraabdominal bleeding (n=5), AD (n=5), fascial dehiscence (n=3), inadvertent enterotomies (n=2), bleeding duodenal ulcer (n=1), bleeding colonic ulcer (n=1), and small bowel obstruction (n=1). Median interval for initial reoperation was 5 days (range, 1–16).

Anastomotic Dehiscence (AD)

AD was detected at a median of 8 days (range, 3–30) postoperatively in 11 patients (10%); these presented after TI takedown in six and TC in five.

Management of AD included reoperations in five patients that developed systemic signs of sepsis; another patient with sepsis died before reoperation due to cardiac failure. Three patients developed an enterocutaneous fistula (ECF) and were treated conservatively. The other two patients suffered AD after relaparotomy for IA bleeding; one of them developed an ECF that was also managed conservatively, and the other patient developed abdominal sepsis and renal failure and eventually died.

Uni- and multivariate analysis of factors related to AD are shown in Table 3. Preoperative hemoglobin <13 g/dl (p<0.02), age ≥50 years (p<0.05), ASA score III vs I/II (p<0.01), history of chronic renal failure (p<0.03), diffuse peritonitis (p<0.05), and open-abdomen management (p< 0.05) were identified through univariate analysis as factors that favored AD. After multivariate analysis, only age ≥50 years was found to be an independent factor related to AD. Risk of developing AD was 13 times higher for this group of older patients. Three of 11 patients (27%) with AD ultimately died.

Besides the aforementioned four patients that developed ECF due to AD, another patient developed it after an inadvertent enterotomy, for a total of five patients (5%) with ECF after TI (n=2) and TC (n=3) reversal. Clinically, they presented 15 days (range, 8–30) after stomal closure. All these ECF had low output and closed spontaneously after 10 days (range, 7–177) of conservative treatment. None of these patients died.

Mortality

A total of seven patients (6%) died. Main causes of death included abdominal sepsis (n=3), pneumonia (n=3), and cardiac failure (n=1).

Several variables were significantly associated with mortality through univariate analysis, which included preoperative hemoglobin <13 g/dl (p<0.05), age ≥65 years (p<0.02), ASA score III vs I/II (p<0.01), use of preoperative TPN (p<0.02), ostomy takedown done <3 months after its construction (p<0.01), reoperation (p<0.01), and AD (p<0.01). After multivariate analysis however, only reoperation (p<0.05) and takedown earlier than 3 months

Table 3 Factors Associated with Anastomotic Dehiscence in 108 Patients After End-Ileostomy or End-Colostomy Takedown (Uni- and Multivariate Analysis)

	No dehiscence (n=97)	Anastomotic dehiscence (n=11)	Univariate analysis p value	Multivariate analysis p value	OR (95% CI)
Site					
Ileostomy	48	6	0.75	NS	NS
Colostomy	49	5			
Site of initial pathology					
Ileum	28	5	0.25	NS	NS
Appendix	17	2			
Colon	52	4			
Origin of patient					
Other hospital	74 (76%)	8 (72%)	0.91	NS	NS
Same (our) hospital	23 (24%)	3 (27%)			
Age ≥50 years	56 (58%)	10 (90%)	<0.05	0.03	13.6 (1.2–148)
Comorbidities	33 (34%)	6 (54%)	0.31	NS	NS
Cardiopathy (various)	6 (6%)	1 (9%)	0.78	NS	NS
Diabetes uncomplicated	8 (8%)	2 (18%)	0.59	NS	NS
Hypertension	31 (32%)	4 (36%)	0.96	NS	NS
Solid tumor without metastasis	1 (1%)	1 (9%)	0.48	NS	NS
Renal failure	1 (1%)	2 (18%)	0.03	0.36	NS
Hypothyroidism	2 (2%)	0 (0%)	0.48	NS	NS
Chronic pulmonary disease	1 (%)	0 (0%)	0.18	NS	NS
Number of surgeries required for control of sepsis, mean (SD)	2.13 (1.7)	2.36 (1.1)	0.67	NS	NS
History of diffuse peritonitis	65 (67%)	11 (100%)	<0.05	0.99	NS
History of open-abdomen management	32 (33%)	7 (63%)	<0.05	0.14	NS
Steroid use	1 (1%)	1 (9%)	0.48	NS	NS
ASA score					
I/II	81 (82%)	5 (45%)	0.003	0.81	NS
III	16 (17%)	6 (54%)			
Preoperative hemoglobin <13 g/dl	41 (42%)	9 (82%)	0.02	0.08	NS
Preoperative total number of lymphocytes/ mm^3, mean (SD)	1,954 (864)	1,686 (292)	0.84	NS	NS
Preoperative serum albumin (g/dl), mean (SD)	3.72 (0.5)	3.78 (0.6)	0.71	NS	NS
Preoperative TPN	9 (9%)	2 (18%)	0.35	NS	NS
Closure <3 months	15 (15%)	1 (9%)	0.57	NS	NS
Intraoperative blood loss	275 (230)	191 (107)	0.23	NS	NS
Intraoperative RBC transfusion	4 (4%)	0 (0%)	0.87	NS	NS
Stapled anastomosis	22 (22%)	2 (18%)	0.96	NS	NS

OD odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists score, *RBC* red blood cell, *TPN* total parenteral nutrition

after its creation (p<0.05) prevailed as independent significant factors (Table 4).

Odds ratios for these subgroups of patients demonstrated that the risk of dying was 58 times higher for patients whose ostomies were closed <3 months after its construction and 23 times higher for patients that had to be reoperated after stomal closure.

Even though reoperation (after stomal closure) was not an endpoint of our study, since it turned out as a significant independent factor related to mortality, we decided to analyze which factors were related to it and found that these reoperations were significantly associated to preoperative hemoglobin <13 g/dl (p<0.02), history of any (not individually) of included comorbidities (p<0.02), and reversal of TI (p<0.04). Also, there were significantly more operations during SSP management for those patients needing a reoperation after ostomy reversal (mean and (SD) of 3.22 (±3.19) vs 1.94 (±1.10), (p<0.003)).

Since the pathophysiology of ischemic colitis is clearly different from that of other causes of SSP, we performed an analysis without the ischemic colitis patients (n=4). No difference was found regarding factors associated with either AD or mortality.

Table 4 Factors Associated with Mortality in 108 Patients After End-Ileostomy or End-Colostomy Takedown (Uni- and Multivariate Analysis)

	Survivors (n=101)	Death (n=7)	Univariate analysis p value	Multivariate analysis p value	OR (95% CI)
Site					
Ileostomy	49	5	0.43	NS	NS
Colostomy	52	2			
Site of initial pathology					
Ileum	29	4	0.81	NS	NS
Appendix	18	1			
Colon	54	2			
Origin of patient					
Other hospital	76 (75%)	6 (85%)	0.86	NS	NS
Same (our) hospital	25 (25%)	1 (14%)			
Age ≥65 years	29 (29%)	5 (71%)	0.02	0.06	NS
Comorbidities	35 (35%)	4 (57%)	0.43	NS	NS
Cardiopathy (various)	6 (6%)	1 (14%)	0.94	NS	NS
Diabetes uncomplicated	8 (8%)	2 (28%)	0.25	NS	NS
Hypertension	33 (33%)	2 (28%)	0.85	NS	NS
Solid tumor without metastases	1 (1%)	1 (14%)	0.28	NS	NS
Renal failure	2 (2%)	1 (14%)	0.46	NS	NS
Hypothyroidism	2 (2%)	0 (0%)	0.28	NS	NS
Chronic pulmonary disease	1 (1%)	0 (0%)	0.07	NS	NS
Number of surgeries required for control of sepsis, mean (SD)	2.16 (1.7)	2.14 (0.9)	0.98	NS	NS
History of diffuse peritonitis	70 (70%)	6 (85%)	0.62	NS	NS
History of open-abdomen management	36 (36%)	3 (41%)	0.98	NS	NS
Steroid use	1 (1%)	1 (14%)	0.28	NS	NS
ASA score					
I/II	84 (84%)	2 (28%)	0.001	0.44	NS
III	17 (17%)	5 (71%)			
Preoperative hemoglobin <13 g/dl	44 (44%)	6 (85%)	<0.05	0.70	NS
Preoperative total number of lymphocytes/mm^3, mean (SD)	1,966 (836)	1,368 (413)	0.24	NS	NS
Preoperative serum albumin, mean (SD)	3.49 (0.6)	3.69 (0.44)	0.85	NS	NS
Preoperative use of TPN	8 (8%)	3 (41%)	0.02	0.82	NS
Takedown at <3 months	12 (12%)	4 (57%)	<0.01	<0.05	58.0 (1.2–3,273)
Intraoperative blood loss	273 (227)	175 (44)	0.26	NS	NS
Intraoperative RBC transfusion	4 (4%)	0 (0%)	0.61	NS	NS
Stapled anastomosis	22 (22%)	2 (28%)	0.96	NS	NS
Reoperation	14 (14%)	4 (57%)	0.02	<0.05	23.0 (1.02–578)
Anastomotic dehiscence	8 (8%)	3 (41%)	0.02	0.343	NS

OD odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists score, *RBC* red blood cell, *TPN* total parenteral nutrition

Discussion

Initial management of SSP includes diagnosis, resuscitation, and antibiotic support. Successful outcome however is contingent upon optimal source control accompanied by adequate drainage and debridement in order to prevent further contamination.[1]

For difficult IA infections, complete control of the focus of infection usually requires aggressive surgical treatment, which in many instances, involves one or more bowel resections. Decision on how to proceed after resection must be made on an individual basis considering several disease and patient and surgical variables in order to minimize the risk of complications.[1]

Postoperative peritonitis requiring reoperation is a serious condition associated with an extremely high mortality rate.[1–4] Thus, most authors agree on avoiding primary anastomosis due to an unacceptable high risk of leakage. Some suggest adding a diverting proximal stoma if an intestinal suture line is fixed under these circumstances.[1,5,6] Others, however, stress the importance of avoiding any intestinal suture with severe peritonitis, even in the presence of a proximal diverting stoma,[6] and suggest exteriorization of the leaking intestinal segment whenever possible.[7,8]

Location for exteriorization depends largely on the affected segment and the procedure being performed. Patient's requirements for both hydro-electrolytical and nutritional supportive measures are progressively increased as stoma location becomes more proximal.[9]

Type of stoma (loop vs end) depends primarily on its functional purpose and the type of operation being performed. The former are mainly used as proximal diversions for protection of distal anastomosis (such as ileo-anal joins), usually done in an elective setting.[8,10,11] The latter are used after bowel has been resected, and the surgeon wants to fully avoid risks of performing a primary anastomosis, usually in the setting of an unstable patient undergoing urgent operations.[12–15]

Literature has largely dealt with loop ostomies. Their closure seems to be technically easier as most can be approached locally, decreasing blood loss and operative time; moreover, reversal is usually planned 6 to 8 weeks after being done.[8,10] Restoration of intestinal continuity after terminal stomas is generally more complex, usually requiring a midline laparotomy with exploration of the entire cavity in many instances. Since both type of patient and difficulties in stoma reversal are quite different, we specifically did not include patients with loop ostomies in this study. Whether this latter could have been performed instead of a TI or TC in any particular case in our series is difficult to assess and not part of the scope of this study, especially since most patients were referred to us after surgical treatment for SSP had already started.

Our study includes patients who were submitted to TI or TC during urgent operative procedures for SSP; once this latter was solved and patients had regained their functional status, they were reoperated to restore intestinal continuity. The downside of avoiding primary anastomosis by performing terminal ostomies is that for those who survive, a new and technically demanding reoperation will be required if gut integrity is wanted. Our aim was to identify risk factors for AD and mortality focusing on this latter operation.

Although some required TPN support prior to ostomy closure, no difference was found on nutritional parameters emphasizing the fact that all were eventually submitted to an operation in essentially the same nutritional status.

In regards to the operative management for SSP, IA hypertension caused by edema and fluid accumulation can lead to an abdominal compartment syndrome. A surgical alternative for this situation is the open-abdomen management. It facilitates easy reexploration and sometimes even, enteral reconstruction if a primary anastomosis was avoided in severely infected abdominal cavities.

Several nonrandomized studies have suggested a higher complication rate for patients with an open-abdomen management. In the only randomized study published to date, we demonstrated closed management of the abdomen to be a more rational approach for the operative treatment of SSP and suggested that the open-abdomen alternative should be used judiciously and selectively, because putative benefits were not clearly observed, and there was a higher risk for morbidity and mortality.[16]

Overall, need for an open-abdomen management in secondary peritonitis is ~10%.[3] In our group of patients with SSP, it was used in 36%. As mentioned, most of our patients were referred from other institutions, and it is impossible to judge if this approach has been used indiscriminately. Noteworthy was the fact that median number of operations required to achieve source control was significantly higher for patients who were managed with an open abdomen (3 (range, 1–15) vs 1 (range, 1–3)) and mean (SD) of 3.28 (±2.28) vs 1.52 (±0.68), ($p<0.001$).This stresses the relationship between increased number of operations and need for an open-abdomen management.

Timing for Stomal Closure

Once SSP has been treated and with full recovery of the patient, a decision must be reached over whether to takedown or leave the stoma and when to do it. Interestingly, ~20%–40% of "temporary" ostomies are never reversed.[5,17–19]

We found that age was related to both AD and mortality. This has also been reported in other studies.[12,13,15,20] It may be that several of these temporary ostomies, which are never reversed, are done in older patients in whom surgical risk is markedly elevated.[13,20]

Timing for reversal is an important and controversial issue. Although some have reported that morbidity and mortality was not affected in selected cases that underwent takedown during the first 10 days,[21] several authors have found stomal closure after 12 weeks yields better results.[11,17] We found that reversal during the first 3 months was an independent factor associated with mortality. This may be explained by the fact that reoperations in patients after sepsis and multiple laparotomies are technically demanding due to development of multiple firm adhesions and sometimes even a "frozen" abdomen, which in turn may lead to a higher rate of complications.[14,17] Moreover, longer intervals between control of SSP and stomal reversal will allow patients to completely recover and regain their functional premorbid status, which will increase their chance of a better outcome.

In spite of these theoretical advantages, it was interesting to find that although not statistically significant, patients whose stomas were not reversed for more than 1 year had an AD rate of 26% (five in 19 patients). This has been also

reported previously.[6,13] To explain this, we hypothesize that factors withholding stomal closure such as advanced age, uncontrolled comorbidities, and long recovery periods from SSP also increase complication rates once restoration of gut integrity is finally decided upon.

Anastomotic Dehiscence

The most feared complication after stoma reversal is AD. Our rate (10%) may seem high when compared to other studies.[6,7,10,14] It should be kept in mind, however, that most of these studies deal with loop stomas created during elective operations with their attendant lower morbidity.[5,8,17] In our series, history of diffuse peritonitis and open-abdomen management were related to AD after ostomy reversal. Both factors may indicate a more severe course of disease, which ultimately required a more aggressive treatment in the form of relaparotomies and leaving an open abdomen during management of SSP.

Association of AD with lower preoperative hemoglobin values suggests that although clinically the patient may seem fit for reoperation, full recovery from previous illness was not yet achieved as manifested by biochemical parameters.

AD was related to higher ASA scores (III vs I/II) through univariate analysis. This also has been found by other authors.[6,14]

Two out of three patients with a history of chronic renal failure developed AD; although association was significant through univariate analysis, numbers are few to reach any firm conclusions.

Enterocutaneous Fistulas

A distinction should be made between AD with IA sepsis and AD progressing into an external ECF. In general for this latter, absence of significant sepsis allows conservative therapy as the initial treatment of choice, surgery being reserved for patients in whom the fistula has not healed ~6 weeks after non-surgical treatment and/or in whom local conditions preclude spontaneous closure. We recently published our experience with 174 patients with postoperative ECF, which mostly originated in the small and large bowel and found high output, jejunal site, multiple fistulas, and sepsis as independent adverse factors related to non-spontaneous closure, need for operative treatment, and death.[22]

In our current series, development of ECF was a clear sign of a controlled AD, since it was not associated to mortality, and conservative management led to spontaneous closure in all. Sepsis responses after AD on the other hand led to reoperations and represented an ominous sign for the patient, as four out of seven patients (57%) ultimately died.

Mortality

Mortality rate in our study (6%) is within range of those reported elsewhere.[7,13,20,23,24]

Mortality according to stomal location (TI vs TC) was not significantly different in our group of patients. This is in contrast to other studies where controversial results have been found and preclude favoring either one.[5,23–25]

Use of preoperative TPN was associated with mortality. High stomal output increases probability of hydro-electrolytic and nutritional complications[9]; these may be exacerbated and more harmful for older patients. A clinical scenario with potentially bad outcomes in this setting is when the older patient who, in spite of TPN support, has an uncontrollable high output ostomy and thus is taken for stomal closure "earlier" than originally planned and not in optimal functional status.

As for AD, mortality was also related to higher ASA scores (III vs I/II) through univariate analysis. In spite that this is an expected finding, we have not found this relationship previously published for this group of patients.

As reported by others,[7] we found patients with AD and reoperation to have higher mortality rates. The need for reoperation for stomal closure also prevailed as a significant independent factor after multivariate analysis.

Timing for stomal closure was the only independent factor associated with mortality where a more practical recommendation can be made. Although a surgeon's decision are based in several disease and patient's and operative variables, withholding restoration for at least 3 months following complete control of SSP seems to offer the best results. As previously mentioned, putative benefits include the encounter with a "friendlier" abdomen and a fit and recovered patient.

In summary, timely and accurate diagnosis, vigorous resuscitation, and antibiotic support are part of the initial management for patients with SSP. Successful outcomes, however, are largely dependent on adequate source control. Aggressive surgical treatment is frequently needed and may include bowel resections and exteriorization in order to avoid risks of primary anastomosis. Once control of SSP is gained and with complete patient recovery, a decision must be reached over whether ostomy reversal is possible and its best timing.

In the presented series of 108 consecutive patients submitted to restoration of intestinal continuity, AD and mortality occurred in 10% and 6%, respectively. We identified several factors associated to them, which included variables related to the patient (age, comorbidities, biochemical parameters), original disease and its treatment (diffuse peritonitis, open-abdomen management, use of TPN), and the operation for stomal closure itself (interval from ostomy creation to closure <3 months, AD, need for reoperations).

Terminal stomas are a valid option for patients with SSP who require aggressive surgical treatment and bowel resections. Restoration of intestinal continuity must be decided upon by both patient and surgeon taking into consideration factors, which influence outcomes. Our findings might allow and help in a better decision-making process.

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J Gastrointest Surg (2008) 12:2119–2124
DOI 10.1007/s11605-008-0685-6

Looking Beyond Age and Co-morbidities as Predictors of Outcomes in Paraesophageal Hernia Repair

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Received: 18 June 2008 / Accepted: 20 August 2008 / Published online: 10 October 2008

Abstract
Introduction Paraesophageal hernia (PEH) repair is a technically challenging operation. These patients are typically older and have more co-morbidities than patients undergoing anti-reflux operations for gastroesophageal reflux disease (GERD), and these factors are usually cited as the reason for worse outcomes for PEH patients. Clinically, it would be useful to identify potentially modifiable variables leading to improved outcomes.
Methods We performed a retrospective analysis of a representative sample from 37 states, using the Nationwide Inpatient Sample database over a 5-year period (2001–2005). Patients undergoing any anti-reflux operation with or without hiatal hernia repair were included, and comparison was made based on primary diagnoses of PEH or GERD. Exclusion criteria were diagnosis codes not associated with reflux disease or diaphragmatic hernia, emergency admissions, and age <18. Primary outcome was in-hospital mortality. Two sets of multivariate analyses were performed; one set adjusting for pre-treatment variables (age, gender, race, Charlson Comorbidity Index, hospital teaching status, hospital volume of anti-reflux surgery, calendar year) and a second set adjusting further for post-operative complications (splenectomy, esophageal laceration, pneumothorax, hemorrhage, cardiac, pulmonary, and thromboembolic events, (VTE)).
Results Of the 23,458 patients, 6,706 patients had PEH. PEH patients are older (60.4 vs. 49.1, $p<0.001$) and have significantly more co-morbidities than GERD patients. On multivariate analysis, adjusting for pre-treatment variables, PEH patients are more likely to die and have significantly worse outcomes than GERD patients. However, further adjustment for pulmonary complications, VTE, and hemorrhage eliminates the mortality difference between PEH and GERD patients, while adjustment for cardiac complications or pneumothorax did not eliminate the difference.
Conclusions While PEH patients have worse post-operative outcomes than GERD patients, we note that differences in mortality are explained by pulmonary complications, VTE, and hemorrhage. The impact of hemorrhagic complications on this group underscores the importance of careful dissection. Additionally, age and co-morbidities alone should not preclude a patient from PEH repair; rather, attention should be focused on peri-operative optimization of pulmonary status and prophylaxis of thromboembolic events.

Keywords Paraesophageal hernia · Hiatal hernia · GERD · Gastroesophageal reflux disease · Nissen fundoplication · Anti-reflux · Surgical outcomes

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Introduction

Paraesophageal hernia (PEH) is defined as a protrusion of the gastric fundus through the diaphragmatic hiatus while the lower esophageal sphincter remains in its normal anatomic position (type II hiatal hernia).[1] In a type III hiatal hernia, both the fundus and the lower esophageal sphincter herniate into the thorax. The majority of PEHs are actually type III (90%).[2] PEHs account for only 5–10% of all hiatal hernias; yet, they are important because they represent a potentially serious disease. The majority of

PEHs are asymptomatic but they do pose a significant risk for the patient in terms of life threatening complications including hemorrhage, strangulation, volvulus, and perforation. In the past, surgeons agreed that once diagnosed, regardless of presence or absence of symptoms, a PEH should be repaired.[3] Recent data has shown that a more selective approach may be implemented when considering surgical repair of PEH.[4]

PEH repair is a technically challenging operation. This may be due to the large amount of herniated contents, need for reduction and resection of a large hernia sac, consideration of a potentially fore-shortened esophagus, and the need to close a large hiatal defect.[2,3] Considerable debate exists regarding the technical specifics of this operation. The relative heterogeneity in technique has resulted in numerous studies, institutional series, and reports in the literature. There is an ongoing effort to identify and establish uniform technique(s) that would ideally result in improved outcomes in terms of recurrence and other quality-of-life outcome variables. Despite the differences in techniques, it seems that the laparoscopic approach to PEH repair and management of GERD has replaced open repair.[4–9]

PEH patients are typically older with more co-morbidities than patients undergoing anti-reflux operations for gastroesophageal reflux disease (GERD).[2,3,5] Based on these observations, it makes intuitive sense that PEH patients may have worse outcomes compared to GERD patients undergoing similar foregut surgery. It is a generally accepted surgical dogma that older patients and those with co-morbidities are subjected to a potentially higher surgical risk. However, there is a paucity of statistically rigorous studies that examine the relationship between traditional surgical risk factors (such as age and co-morbidities) and clinical outcomes in patients undergoing foregut surgery for PEH or GERD on the population level. It would be useful to identify specific variables in an effort to improve selection, risk stratification, and optimization of patient outcomes. The purpose of this study is two-fold: to better characterize PEH patients compared to GERD patients undergoing foregut surgery and to identify any potentially modifiable risk factors to improve outcomes.

Methods

Data Source

We performed a retrospective analysis of a representative sample from 37 states using the Nationwide Inpatient Sample (NIS) database over a 5-year period (2001–2005). The NIS compiles discharge data from inpatient hospitalizations from 20% of all hospitals from 37 participating states, maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project-3. It consists of roughly 7 million patient discharge records per year, originating from approximately 1,000 different hospitals per year, although not necessarily the same hospitals each year. Data available within the NIS include patient and hospital demographics, payer information, treatment and concomitant diagnoses, inpatient procedures, inpatient mortality, and length of stay. The Johns Hopkins Institutional Review Board deemed this public-domain anonymous data set as exempt from review.

Patient Selection

Patients undergoing any anti-reflux operation with or without PEH repair were included in the analysis. Comparison was made based on primary diagnoses of PEH or GERD. This was accomplished by searching for the relevant ICD-9 diagnosis and procedure codes (Table 1). ICD-9 codes 44.65, 44.66, and 44.67 were used to identify patients who underwent an anti-reflux procedure. Since code 44.65 is a very general description, we included any records with this code (44.65) only if they also included diagnosis codes for esophagitis, gastroesophageal reflux, esophageal ulcer, diaphragmatic hernia and diaphragmatic hernia with obstruction (530.10, 530.11, 530.19, 530.81, 530.20, 553.3, 552.3). Procedure codes associated with a code for thoracic repair of diaphragmatic hernia (530.8) were excluded from our analysis as well. For all procedure codes, esophageal cancer (150.0–150.5, 150.8–150.9) and gangrene (551.3) were excluded. Other exclusion criteria included emergency admissions and age <18. Our primary outcome was in-hospital mortality.

Statistical Analysis

Two sets of multivariate analyses were performed. The first set adjusted for pre-treatment variables—age, gender, race,

Table 1 ICD-9 Codes Used for Patient Selection

Code	Description
44.65	Esophagogastroplasty
44.66	Esophagogastric sphincteric competence
44.67	Same as above, laparoscopic
530.10	Esophagitis
530.11	Reflux esophagitis
530.19	Other esophagitis
530.20	Ulcer of esophagus without bleeding
530.81	Esophageal reflux
553.3	Diaphragmatic hernia
530.0	Achalasia and cardiospasm
552.3	Diaphragmatic hernia with obstruction
551.3	Diaphragmatic hernia with gangrene

Charlson score, hospital teaching status, hospital volume of anti-reflux surgery, and calendar year. The second set adjusted for peri-operative complications—splenectomy, esophageal laceration, pneumothorax, hemorrhage, cardiac, pulmonary, and thromboembolic events (VTE).[10]

Analysis was performed using the software package STATA/MP 10 (College Station, Texas). Bivariate analysis of categorical data was performed using the Chi-Squared test. Analysis of continuous data was performed using the Student's *t* test. Multivariate analysis was performed using multiple logistic regression models, adjusting for age, gender, race, Charlson score, hospital teaching status, elective status, year of procedure, and type of procedure. A p value of <0.05 was considered to be statistically significant.

Results

Patient Characteristics

Patients (23,458) underwent foregut surgery for GERD and/or PEH. In the univariate analysis, of the 23,458 patients, 6,706 (28.6%) patients had PEH. The mean age of patients was 52.3 (median age was 52); 14,670 (62.8%) patients were women; 14,111 (87.9%) patients were white, 676 (4.21%) black, and 838 Hispanic (5.22%); 10,921 patients (46.6%) were treated at teaching hospitals (Table 2). In-hospital mortality for all patients was 0.38% (88 patients). Two hundred twenty-nine (0.98%) patients required splenectomy; 132 (0.56%) patients underwent laceration repair; 210 (0.90%) patients were diagnosed with pneumothorax; 1,549 (6.6%) patients underwent unexpected re-operation; 594 (2.53%) patients experienced hemorrhagic complications; 157 patients (0.67%) had wound-related complications; 703 (3%) patients had obstructive complications; 1,007 (4.29%) patients had pulmonary complications; 254 (1.08%) had cardiac complications; 111 (0.47%) patients had thromboembolic complications. Mean length of stay was 3.4 days with a median of 2 days (Table 2).

Table 2 Univariate Analysis: Patient Demographics and Adverse Outcomes—All Patients

Variable	*N*	%
All patients (total *N*)	23,458	
PEH	6,706	28.6
Age in years	52.3 (mean)	52 (median)
Female gender	14,670	62.8
Race—White	14,111	87.9
Race—Black	676	4.21
Race—Hispanic	838	5.22
Teaching hospital	10,921	46.6
In-hospital mortality all patients	88	0.38
Splenectomy	229	0.98
Laceration repair	132	0.56
Pneumothorax	210	0.90
Unexpected re-op	1,549	6.6
Hemorrhagic	594	2.53
Wound related	157	0.67
Obstructive	703	3
Pulmonary	1,007	4.29
Cardiac	254	1.08
Thromboembolic	111	0.47
LOS in days	3.4 (mean)	2 (median)

LOS Length of stay

PEH vs. GERD Patients

On bivariate analysis, PEH patients were significantly older (60.5 vs. 49.1, $p<0.001$). A significantly higher percentage of PEH patients were women (68.3% vs. 60.52%, $p<0.001$). Mean length of stay was significantly higher for PEH patients (Table 3).

PEH patients were more likely to die than those without PEH (0.75% vs. 0.23%, $p<0.001$). Patients with PEH had a significantly higher risk of undergoing splenectomy (1.52% vs. 0.76%, $p<0.001$). Similarly, these patients had a significantly higher proportion of laceration repair, pneumothorax, pulmonary complications, cardiac complications, thromboembolic, and hemorrhagic complications (Table 3).

The first set of multivariate analyses, adjusting for pre-treatment variables (age, gender, race, Charlson score, hospital teaching status, hospital volume of anti-reflux surgery, and calendar year), demonstrates that PEH patients are more likely to die and have a significantly higher likelihood of complications compared to GERD patients (Table 4).

In the second multivariate analysis, the previously noted difference in mortality between PEH and GERD is maintained when adjusting for splenectomy ($p<0.043$), laceration

Table 3 Bivariate Analysis: Patient Demographics and Adverse Outcomes—PEH & GERD

Variable	GERD *N* (%)	PEH *N* (%)	*p* value
Age in years (mean)	49.1 (mean)	60.5 (mean)	<0.001
Female gender	10099 (60.52)	4571 (68.3)	<0.001
LOS in days (mean)	3.01 (mean)	4.32 (mean)	<0.001
Mortality	38 (0.23)	50 (0.75)	<0.001
Splenectomy	127 (0.76)	102 (1.52)	<0.001
Laceration repair	59 (0.35)	73 (1.09)	<0.001
Pneumothorax	107 (0.64)	103 (1.54)	<0.001
Pulmonary	575 (3.43)	432 (6.44)	<0.001
Cardiac	118 (0.70)	136 (2.03)	<0.001
Thromboembolic	51 (0.30)	60 (0.89)	<0.001
Hemorrhagic	343 (2.05)	251 (3.74)	<0.001

Table 4 Multivariate Analysis: Odds Ratio of Adverse Events in PEH vs. GERD Undergoing Foregut Surgery

	Adverse event	Odds ratio (95% CI)	*p* value
	Mortality	1.81 (1.06–3.09)	0.030
Technical	Laceration repair	2.00 (1.29–3.10)	0.002
	Splenectomy	1.44 (1.03–2.01)	0.033
	Pneumothorax	2.45 (1.64–3.65)	0.000
	Hemorrhagic	1.53 (1.22–1.92)	0.000
Peri-op	Pulmonary	1.48 (1.26–1.75)	0.000
	Cardiac	2.11 (1.43–3.11)	0.000
	Thromboembolic	2.34 (1.29–4.23)	0.005

repair ($p<0.028$), pneumothorax ($p<0.034$), and cardiac complications ($p<0.04$). This effect is lost when adjusting for pulmonary ($p=0.079$), hemorrhagic ($p=0.106$), and VTE ($p=0.05$) complications.

Discussion

PEH is a disease that poses unique clinical challenges. Despite its apparent benignity, it has the potential for severe complications. The actual mechanistic sequence of events leading to the development of PEH is not completely understood. It is likely that the process involves stretching of the phrenoesophageal membrane and attendant weakening and enlargement of the diaphragmatic hiatus.[3,11] This process likely evolves with increasing age.[3] Patients may present with heartburn, regurgitation, post-prandial fullness, chest pain, dysphagia, as well as signs and symptoms suggestive of anemia.

PEH repair continues to raise controversy and questions—ranging from the indications for surgery to the actual technical specifics of the operation. These questions have engendered many good studies examining the experience and outcomes of various institutes. Almost all of these single-center series have consistently observed that PEH patients tend to be older, with more co-morbidities. Gangopadhyay et al. examined the relationship between age, co-morbidities, and PEH in their 2006 paper.[2] However, they determined that complication rates are higher in elderly patients. Brunt et al. examined outcomes in elderly patients undergoing laparoscopic anti-reflux surgery for patients with type 1 hiatal hernias and compared them to younger patients.[12] Even though type 1 hiatal hernias are not as complex as PEHs, they noted that elderly patients had more minor complications compared to younger patients, and that there was no increase in major complications.[12] Flum et al. studied outcomes in patients undergoing anti-reflux surgery on a population level, perhaps one of the few such studies in the literature to date.[13] They observed that nationally, even though morbidity and mortality associated with anti-reflux surgery performed in the 1990s was quite low, it was still higher than suggested by case series. Further, they noted that surgeon experience with the procedure was linked to better outcomes. This relationship has been demonstrated by other authors reviewing their results for anti-reflux surgery,[14–16] as well as in other advanced laparoscopic surgical procedures.[17–19]

In our study, 28.6% of the NIS cohort underwent foregut surgery for PEH. The overall in-hospital mortality was quite low—0.38%. As noted, complication rates were also quite low. When we compared PEH to GERD patients in our bivariate analysis, several interesting observations were noted. First, PEH patients were significantly older than GERD patients—60.5 vs. 49.1. This is similar to what has been reported in the literature.[3,20] PEH is an insidious condition. Clinically, patients with PEH may be asymptomatic and may in fact be unaware of the fact that they even have a PEH for many years. More often, they may be tolerating a variety of vague, nondescript symptoms for many years prior to diagnosis.[3] The delayed presentation and progress of symptoms may explain the difference in age. Even though the overall mortality for PEH patients was low (0.75%), it was significantly higher than GERD patients (0.23%). It is interesting to note that a significantly higher percentage of the PEH patients were women when compared to the GERD group (68.3% vs. 60.52%, $p<0.0001$). Overall, on univariate analysis, women make up the majority of the cohort (62.8%). This has been observed in other series as well.[2,3,21] Several studies in the cardiac, obstetric and geriatric literature have demonstrated that women tend to live longer than men, attributable to vascular, hormonal and genetic differences.[22] This, coupled with the fact that PEH may not be diagnosed or symptomatic until the later years in life, may explain, in part, why PEH patients are older and tend to be women. PEH patients had a significantly longer mean length of stay in hospital than their GERD counterparts—mean of 4.32 vs. 3.01 days, $p<0.001$. Similar trends have been noted in other studies.

In our first multivariate analysis, the odds of mortality, technical, and peri-operative complications (Table 4) was significantly higher in PEH patients, even adjusting for the effect of hospital case volume. In our second set of multivariate analyses, we wanted to see if our primary outcome, mortality, remained significantly higher in PEH patients after adjusting for our peri-operative complications. The difference in mortality is no longer significant after adjusting for pulmonary complications. Bivariate analysis demonstrates that PEH patients have a significantly higher rate of pulmonary complications (6.44% vs. 3.43%, Table 3; OR 1.48, Table 4). It is also worth noting that on bivariate analysis, pulmonary complications rank first among the list of chosen adverse-outcome variables. An intra-thoracic stomach may affect ventilation and perfusion, and may even make these patients more sensitive to the pneumo-peritoneum.

Further, dissection in the chest/mediastinum through an abdominal/laparoscopic approach is known to be a difficult and complex undertaking that requires a high level of skill and comfort with laparoscopic and foregut surgery, as has been noted elsewhere.

PEH patients have a higher rate of hemorrhagic complications (3.74% vs. 2.05%, OR 1.53). However, when adjusting for this adverse event, the mortality difference is once again eliminated. This underscores, in part, the importance of minimizing intraoperative hemorrhage through careful dissection during this type of advanced laparoscopic procedures. The dissection of the viscera and hernia sac across two domains—the abdomen and the thorax—is indeed a difficult undertaking. There are several important named vessels in this area (i.e., left gastric), as well as the highly vascular spleen, and the short gastrics, which may be difficult to appreciate in a patient with a significant PEH and associated intra-thoracic abdominal viscera. The intra-thoracic stomach itself may be friable and prone to bleeding. The hernia sac itself may also bleed, secondary to long-term inflammatory changes and edema that result.

After adjusting for VTE complications, the mortality difference is also eliminated. While the overall rate of VTE was only 0.47%, on bivariate analysis, patients with PEH had a significantly higher rate (0.89% vs. 0.30%, $p<0.0001$). This compares similarly with multiple single-center series from 1994–1997.[23] DVT and PE following major surgical procedures remain significant causes of major morbidity and mortality. Factors specific to laparoscopic surgery such as carbon dioxide pneumoperitoneum, reverse Trendelenberg position, and increased operative time may increase the risk of DVT development. It is known that the pneumo-peritoneum actually impedes venous return leading to venous stasis. Conversely, the salutary effects of laparoscopic surgery, such as early ambulation and the potential decrease in postoperative hypercoagulation may actually decrease the risk of DVT development.[23] Furthermore, non-operative factors, or patient factors such as age, for example, are known to increase the risk of DVT and PE. PEH patients are significantly older than the GERD patients, but it is likely that age alone is not the sole contributing factor to mortality in these patients.

Conclusion

In an era when health policy and surgical practice is increasingly driven by evidence-based guidelines and outcomes, there is a clear dearth of population-based analyses of outcomes in patients undergoing PEH repair. Single-center series are subject to selection and publication bias and may not accurately reflect the population-level risk of adverse outcomes.[13] Our study is unique in that we attempt to quantify, on a population level, a number of observations: (1) the incidence of adverse events in all patients undergoing foregut surgery for PEH and GERD from 2001–2005; (2) the difference, if any, in demographics and adverse events/outcomes between these patients and (3) if there are any specific features unique to the two cohorts that may explain the difference in outcomes.

There are some inherent limitations in this study. First, since our data is drawn from a large population-based database, it is very difficult to discern the clinical specifics or details associated with each adverse-outcome variable. Second, despite being high-powered in terms of the number of records, it is difficult to make definitive conclusions given the inherent heterogeneity that may exist given the lack of knowledge about the actual technical specifics about the surgical approach, as well as other unique clinical identifiers. Another limitation is our inability to precisely differentiate between laparoscopic and open repairs. This is because there were no specific ICD-9 codes to identify whether anti-reflux procedures were performed laparoscopically before 2004.

In conclusion, albeit low, the incidence of adverse events is significantly higher in PEH patients compared to GERD patients. PEH patients are significantly older, and a significantly higher percentage are women. The most common adverse events were pulmonary and hemorrhagic, both on univariate and bivariate analyses. On multivariate analysis, PEH patients had a significantly higher percentage of pulmonary and hemorrhagic complications. Finally, adjustment for pulmonary, hemorrhagic and VTE complications eliminated the difference in mortality between PEH and GERD patients. Perhaps a combination of improved peri-operative care focusing on pulmonary physiology and respiratory mechanics, improved surgeon experience with principles of laparoscopic PEH repair, concurrent attention to meticulous hemostasis and attention to DVT prophylaxis will continue to improve outcomes, such that age and co-morbidities alone will not preclude PEH repair.

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J Gastrointest Surg (2008) 12:2125–2132
DOI 10.1007/s11605-008-0707-4

After Laparoscopic Heller Myotomy, Do Emergency Department Visits or Readmissions Predict Poor Long-Term Outcomes?

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Received: 4 March 2008 / Accepted: 8 September 2008 / Published online: 15 October 2008

Abstract
Introduction Laparoscopic Heller myotomy is a first-line treatment for achalasia. To improve outcomes after myotomy and to determine if poor early results predict later outcomes, emergency department (ED) visits and readmissions within 60 days following laparoscopic Heller myotomy were studied.
Materials and Methods Since 1992, 352 patients have undergone laparoscopic Heller myotomy and are followed through a prospectively maintained registry. Causes of ED visits and readmissions within 60 days after myotomy were determined. Patients scored their symptoms of achalasia before myotomy and at last follow-up; scores were compared to determine if the reasons leading to ED visits and/or readmissions impacted long-term outcome after myotomy.
Results Fourteen (4%) patients had ED visits, and 18 (5%) patients had readmissions within 60 days following myotomy. Sixty-four percent of ED visits were for dysphagia/vomiting and 36% were for abdominal/chest pain, while 37% of readmissions were for dysphagia/vomiting. Pneumonia was complicated by empyema in four patients, all without leaks; two patients expired. Despite ED visits/readmissions, achalasia symptom (e.g., dysphagia, regurgitation, choking, heartburn, and chest pain) frequency and severity scores improved after myotomy ($p<0.05$ for all).
Conclusions ED visits and readmissions are infrequent following laparoscopic Heller myotomy. ED visits were generally due to complaints related to achalasia or edema after myotomy, while readmissions were generally related to complications of operative intervention or chronic ill health. Despite ED visits or readmissions early after myotomy, symptoms of achalasia are well palliated by myotomy long-term.

Keywords Achalasia · Laparoscopic Heller myotomy · ED visits · Readmissions

Presented at the Society for Surgery of the Alimentary Tract 48th Annual Meeting, Washington, DC, May 19–24, 2007.

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Introduction

Achalasia is an idiopathic primary motility disorder characterized manometrically by incomplete lower esophageal sphincter (LES) relaxation and complete loss of primary peristalsis of the esophagus.[1] Untreated, it may lead to progressive dysphagia, esophageal dilation, stasis, and a poor quality of life. Treatment is palliative and consists of the following: botulinum toxin, which provides temporary inhibition of excitatory cholinergic input to the LES smooth muscle;[2] pneumatic dilation, which causes forceful tearing of the LES smooth muscle;[3] or operative

esophageal myotomy. Over the last decade, laparoscopic approaches to achalasia have become widely available and experience has grown, as documented by favorable results from many centers.[4–11] Laparoscopic Heller myotomy has become the treatment of choice for most patients with symptomatic achalasia, certainly among surgeons[12] and even among gastroenterologists.[13] As well, laparoscopic Heller myotomy is recognized as a definitive therapy for salvage of patients failing endoscopic therapy for achalasia.[14,15]

In 1992, we undertook our first laparoscopic Heller myotomy. We have prospectively followed patients since then, building upon our earlier experience with myotomy via celiotomy or thoracotomy. While our early videoscopic myotomy was undertaken through thoracoscopy, following our initial experience of less than 20 patients, we converted our approach to involve laparoscopy because of perceived simplicity and superior outcomes. Our initial results with thoracoscopy have been documented,[16] and we believed they were inadequate to justify continuing that approach.

Many questions over the past decade have arisen regarding outcomes after laparoscopic Heller myotomy, including the frequency and severity of gastroesophageal reflux, the need for an antireflux fundoplication, the need for intraoperative endoscopy, the extent of myotomy, the long-term relief of dysphagia, the rates of success and failure, and the need for interventions and revisions after myotomy.

This report documents our experience over more than the last decade with emergency department (ED) or hospital admissions soon after (i.e., within 60 days) videoscopic Heller myotomy. In undertaking this review of our experience, we have sought to determine whether poor early results can predict later outcomes by evaluating ED visits and readmissions within 60 days following laparoscopic Heller myotomy. We also believe that, in an effort to improve our results, we should analyze patients suffering early morbidity and suboptimal early results, patients presumably at high-risk to do poorly long term.

We hypothesized before reviewing our cumulative experience that despite reasons for ED visits and/or readmissions early after myotomy, symptoms of achalasia would be well palliated by myotomy long term. As well, for patients experiencing suboptimal outcomes early after myotomy, early results would not condemn patients to suboptimal outcomes long term.

Materials and Methods

Since 1992, 352 patients have undergone laparoscopic Heller myotomy for relief of symptoms of achalasia and are followed in a prospectively maintained registry. Readmissions within 60 days of myotomy were noted; details about the readmissions were recorded. ED visits within 60 days of myotomy, which did not result in a readmission, were documented. ED visits that resulted in a readmission were considered as part of the readmissions process and did not add to the total accounted ED visits. Patient data collection and study design were conducted in concordance with a protocol approved by the institutional review board of the University of South Florida, College of Medicine.

Preoperative Assessment

Preoperatively, the diagnosis of achalasia was made based on manometry, upper gastrointestinal (UGI) studies, timed barium studies, and upper endoscopy. Before myotomy, patients were asked to grade the frequency of symptoms of achalasia, including dysphagia, chest pain, regurgitation, choking, and heartburn utilizing a Likert scale (0=never bothersome; 2=rarely; 4=monthly, 6=weekly, 8=daily; 10=always/every time I eat) (Table 1). Before myotomy, symptom severity was also graded on a Likert scale (0=not bothersome to 10=very bothersome).

Operative Technique

Patients were operated upon using a five-port technique (using four 10-mm trocars and one 5-mm trocar). Concomitant endoscopy was used to guide the extent of the myotomy in all patients to avoid inadequate myotomy in either the cephalad or caudad direction on the esophagus and to avoid an unnecessarily long myotomy on the gastric cardia.[7] Once the obstruction due to achalasia is relieved, it has long been our belief that further myotomy is superfluous, and thereby, risks of extensive myotomy are not justified.

Our specific technique for laparoscopic Heller myotomy with intraoperative endoscopy has been previously

Table 1 Patients were Asked Before and After Laparoscopic Heller Myotomy to Grade the Frequency and Severity of Their Symptoms of Achalasia Utilizing a Likert Scale

How often do you experience:
Food gets stuck
Postprandial chest pain
Forceful vomiting
Regurgitation
Choking
Coughing
Heartburn
Severity of symptoms:
Heartburn postprandial/while sleeping
Nausea/vomiting/regurgitation after meals
Food stuck in throat/chest
Difficulty swallowing
Bitter taste in mouth postprandial/while sleeping
Asthma/coughing
Gas/bloating

described.[17] Anterior fundoplication was initially applied in patients who had a large hiatal hernia and a patulous esophageal hiatus or to buttress the repair of an intraoperative esophagotomy. More recently, concomitant anterior fundoplication has been unitized in all patients undergoing laparoscopic Heller myotomy in response to a randomized clinical trial supporting its routine application.[18] Anterior fundoplications were constructed to bring the anterior fundus of the stomach up and over the anterior esophagus, generally covering most, but not all, of the myotomized segment. The fundus was generally secured with four sutures to esophageal muscle, two on the left side and two on the right side of the myotomy. Then, the esophageal hiatus was sufficiently closed, and the fundoplication was secured to the right crus to relieve tension on the fundoplication or twisting of the distal esophagus.

Myotomy was considered to be adequate once four criteria were met: bright translumination of the myotomized segment crossing the Z-line as seen through both the laparoscope and through the endoscope, prompt opening of the gastroesophageal junction with gentle air insufflation through the endoscope, easy passage of the endoscope into the stomach, and absence of transmural burn or perforation by either direct (visualization with the endoscope or laparoscope) or indirect (presence of bubbles during insufflation through the endoscope while the myotomized segment is under saline irrigant) examination.[7]

Postoperative Assessment

Postoperatively, UGI studies confirmed adequacy of myotomy with esophageal emptying. Again, patients were asked to grade the frequency and severity of symptoms of achalasia (Table 1). As well, patients were asked to grade their overall outcomes as excellent (complete or near complete resolution of symptoms), good (symptoms occurring once per month or less frequently), fair (symptoms weekly or less frequently), or poor (symptoms daily or more often or as severe as before myotomy). They were also asked to grade their experience from very unsatisfying to very satisfying and declare if they would be willing to undergo laparoscopic Heller myotomy again if they knew then what they know now.

Data Management and Statistical Analysis

Data were stored in a Microsoft Excel (Microsoft Corp, Redmond, WA) spreadsheet. Wilcoxon matched-pairs test was utilized for symptom score comparison in Graphpad Instat version 3.06 (Graphpad Software Inc., San Diego, CA). Where appropriate, data are presented as median (mean±standard deviation).

Results

Since 1992, 352 patients have undergone laparoscopic Heller myotomy for the relief of achalasia symptoms and are followed in a prospectively maintained registry (Table 2).

There were 14 ED visits by 14 patients (seven male and seven female) of median age 52 years. ED visits for three patients were after "redo" Heller myotomies. Preoperatively, three patients had five Botox injections, and eight patients had 18 balloon dilations. ED visits were mostly due to intractable vomiting/dysphagia (nine patients) or abdominal/chest pain (five patients) (Table 3).

Nine patients visited the ED complaining of dysphagia and intractable vomiting. These patients (six male and three female) had a median age of 58 years (49 years±19.7). These patients underwent UGI series, which documented no "high-grade" obstruction of food impaction, and those patients were discharged without further interventions.

There were five ED visits for pain (three abdominal and two chest pains). Patients complaining of abdominal pain underwent UGI series, abdominal and chest x-ray, computed tomography (CT) scan of the abdomen and pelvis, electrocardiogram, and hematologic and blood chemistry profiling and were discharged without significant recurrence of pain. One patient who visited the ED for chest pain underwent hematologic and blood chemistry profiling and evaluation of a cardiac source; the pain was relieved with the administration of nitroglycerin before discharge. The second patient who arrived at the ED complaining of chest pain was a patient with a medical history of asthma that underwent a "redo" laparoscopic Heller myotomy. The patient underwent extensive workup in the ED and was found to have an asthma exacerbation. A chest x-ray showed no abnormalities, and the patient complaints of pain were relieved with albuterol administration before discharge.

Follow-up after myotomy in these patients is 33 months (34 months±20.4). Frequency and severity symptom scores of patients with ED visits after myotomy improved postoperatively (Fig. 1). Symptom relief was rated as "excellent" or "good" by 72% (Fig. 2), 85% of patients felt that their overall experience was "very satisfying" or "satisfying" (Fig. 3), and 86% of patients said that they

Table 2 Demographic Data of All Patients Who Have Undergone Laparoscopic Heller Myotomy since 1992

Total number of patients	352 patients
Age (years)	47 years (49 years±18.3)
Gender	56% male/44% female
Duration of symptoms (years)	4 years (7 years±7.4)
Follow-up (months)	26 months (34 months±32.7)

Data is presented as median, (mean±standard deviation), where appropriate.

Table 3 Reasons for Emergency Department Visits and Readmissions

Reasons for emergency department visits	Number of patients	Percent	Reasons for readmissions	Number of patients	Percent
Vomiting/dysphagia	9	2.5	Pneumonia	7	2.0
Abdominal/chest pain	5	1.4	Vomiting/dysphagia	6	1.8
			Abdominal pain	2	0.6
			Ileus/obstruction	2	0.6
			Pneumothorax	1	0.3

would undergo laparoscopic Heller myotomy again if they knew then what they know now.

There were 18 readmissions among nine male and nine female patients of median age 58 years. Length of stay for the readmissions was 5 days (8 days±8.3). Two patients had undergone reoperative Heller myotomies. Twelve of 18 patients were readmitted for pneumonia (seven patients) or intractable dysphagia/vomiting (six patients; Table 3). Follow-up after myotomy in these patients is 26 months (24 months±21.4). Frequency and severity symptom scores of patients with readmissions improved postoperatively (Fig. 4). Symptom relief was rated as "excellent" or "good" by 89% (Fig. 5),89% of patients felt that their overall experience was "very satisfying" or "satisfying" (Fig. 6), and 89% of patients said that they would undergo laparoscopic Heller myotomy again if they knew then what they know now.

Seven patients (two male and five female) of median age 67 years (58 years±27.7) were readmitted for pneumonia. Their median length of stay was 12 days (11 days±8.4). Two of the readmissions were patients that developed empyema and resulted in respiratory failure and death. Neither patient had an esophageal leak at the myotomy site. Two patients readmitted had developed thoracic abscesses and underwent decortications and empyema drainage. One 12-year-old patient was readmitted for aspiration pneumonia and was later discharged after improving without procedural intervention. The last two patients readmitted for pneumonia had uneventful hospital stays and were discharged after antibiotic administration and clinical improvement.

Six patients (one male and five female) of median age 48 years (52 years±13.3) were readmitted for dysphagia/intractable vomiting. Their median length of stay was 2 days (3 days±1.5). One patient, who had undergone a reoperative, or "redo," laparoscopic Heller myotomy, had a twist at the lower esophagus, which may have been a consequence of the anterior fundoplication. This patient underwent a revision of laparoscopic Heller myotomy during the readmission. A second patient underwent "redo" laparoscopic Heller

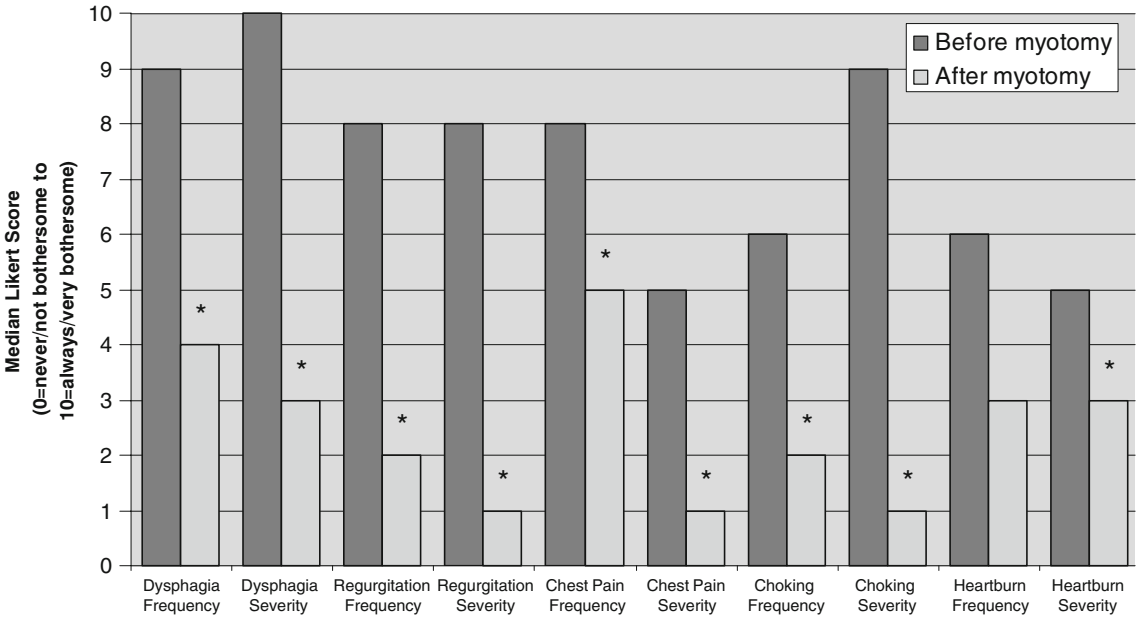

Figure 1 Symptom frequency and severity scores before and with latest follow-up after myotomy for patients with emergency department visits within 60 days following myotomy (n=14). *p<0.05, less in frequency or severity than symptom scores before myotomy, Wilcoxon matched-pairs test.

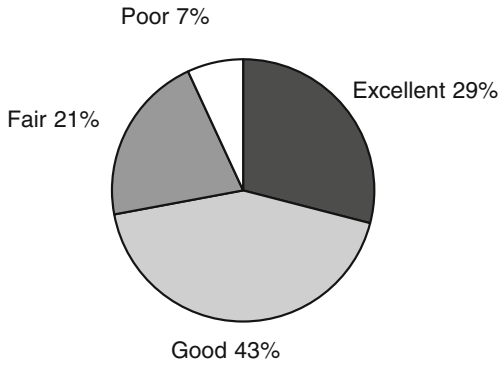

Figure 2 Symptom relief following laparoscopic Heller myotomy was graded by patients with emergency department visits (n=14) at latest follow-up. *Excellent* Nearly/completely resolved symptoms; *good* greatly improved symptoms; *fair* slightly improved symptoms; *poor* no improvement/worsened symptoms.

myotomy for persistent dysphagia. One patient was readmitted twice for dysphagia after myotomy. During the first admission, the patient underwent an upper GI study and required no intervention. However, when the patient was readmitted for the second time, EGD with balloon dilation was undertaken with modest improvement. One patient received a barium swallow upon readmission, and the remaining two patients were discharged without procedural intervention.

Two patients were readmitted for intractable abdominal pain with pneumoperitoneum. One of these patients underwent exploratory celiotomy because of pneumoperitoneum and an impressive abnormal examination. No significant findings were noted and a drain was placed. Nothing drained; the drain was removed in the early postoperative period, and the patient was discharged after clinical improvement. The second patient, initially found to have pneumoperitoneum on an upper GI series, underwent CT scanning that documented no pneumoperitoneum. On the second day of readmission, the patient's abdominal pain resolved; the patient was tolerating liquids and was discharged on the third day of readmission.

One patient was readmitted for pneumothorax and pleural effusion and received a tube thorocostomy during readmission. Another patient was readmitted for small bowel obstruction and underwent bowel resection and was later discharged after clinical improvement. Yet, another patient was readmitted for postoperative ileus and was discharged the next day after resolution of symptoms.

Discussion

We have undertaken a large number of laparoscopic Heller myotomies and have amassed a significant clinical experience with the operative treatment of symptomatic achalasia.[14] This study represents a subset of what might be the largest institutional experience with laparoscopic Heller myotomy. Conventional wisdom would purport that early postoperative ED visits and/or hospital readmissions would result in poorer resolution of symptoms and lower rates of success than Heller myotomies that did not require early ED visits and/or hospital readmissions. This study demonstrates that, contrary to intuition and conventional wisdom, early postoperative ED visits and/or hospital readmissions do not deter from significant and satisfactory long-term palliation of achalasia symptoms by myotomy.

The literature of the last decade has progressive acceptance of Heller myotomy as effective therapy for achalasia when undertaken laparoscopically. While the experience of videoscopic myotomy have been frequently reported, the effect of early postoperative emergency room visits and/or hospital readmissions on long-term outcomes has yet to be studied. We, like others, have reported promising results in our early experience with laparoscopic Heller myotomy and have seen these promising outcomes persist with time.[7,10,14–17] Dramatic relief of symptoms early after laparoscopic Heller myotomy predicts long-term success, and relatively poor relief of symptoms does not necessarily predict a poorer outcome.[19] What has not been reported in the era of laparoscopic Heller myotomy is whether long-term palliation of symptoms of achalasia occurs after laparoscopic Heller myotomy despite significantly poor palliation early after myotomy or appearance of significant new symptoms leading to early postoperative emergency room visits and/or hospital readmissions early after myotomy. This report documents that patients who experience dramatic early postoperative symptoms or complications leading to emergency room visits and/or hospital readmissions have long-term palliation of troubling symptoms of achalasia and have outcomes which, in general, are similar to outcomes of patients who have not experienced those symptoms or complications and/or have not returned to the hospital.

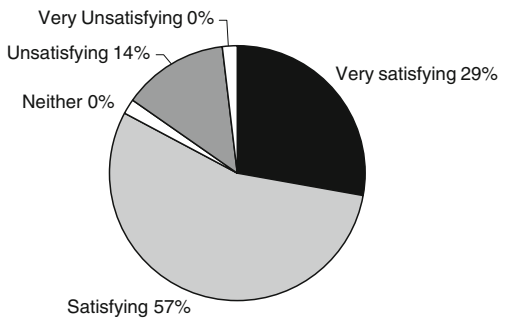

Figure 3 Overall experience of patients that underwent laparoscopic Heller myotomy with emergency department visits (n=14) reported at latest follow-up. Very satisfying, satisfying, neither satisfying nor unsatisfying, unsatisfying, very unsatisfying.

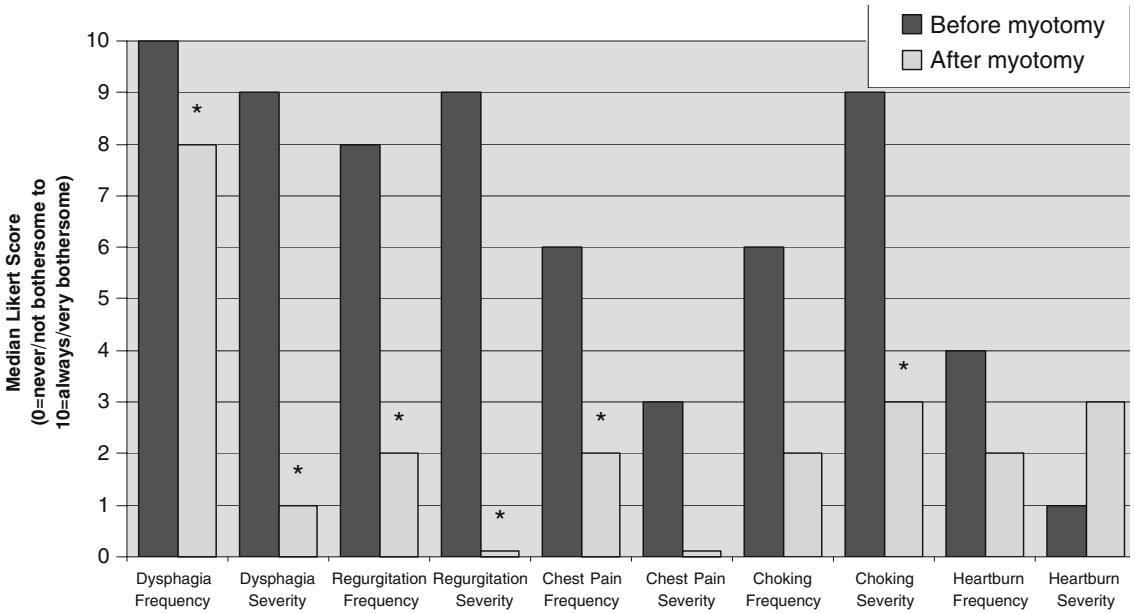

Figure 4 Symptom frequency and severity scores before and with latest follow-up after myotomy for patients with readmissions within 60 days following myotomy (n=18). *p<0.05, less in frequency or severity than symptom scores before myotomy, Wilcoxon matched-pairs test.

Laparoscopic Heller myotomy was completed, in general, with little perioperative morbidity. During the 60-day postoperative period, less than one in ten patients had emergency room visits and/or hospital readmissions with only one in 50 requiring further intervention. They generally presented to the ED with symptoms of esophageal obstruction (e.g., dysphagia or vomiting). When pain led to ED visits, it was not directly due to achalasia or myotomy, but possibly due to either or both. Postoperative vomiting/dysphagia leading to ED visits (and/or hospital readmissions), while distressing to both the patient and surgeons, did not contribute to long-term postoperative morbidity or predict poor palliation of symptoms. All patients who went to the ED postoperatively complaining of vomiting/dysphagia had symptoms that resolved without further intervention. As well, patients who arrived to the emergency room complaining of abdominal/chest pain required only medical therapy, including albuterol nebulizer or administration of nitroglycerin, for complete resolution of symptoms.

Unlike the patients who visited the emergency room and were discharged, nearly half of the patients who were readmitted to the hospital required further intervention. Two patient who presented with dysphagia and intractable vomiting had to undergo "redo" laparoscopic Heller myotomy and another underwent esophagogastroduodenoscopy with balloon dilation due to inadequate relief of symptoms. Whether the myotomy was inadequate or not

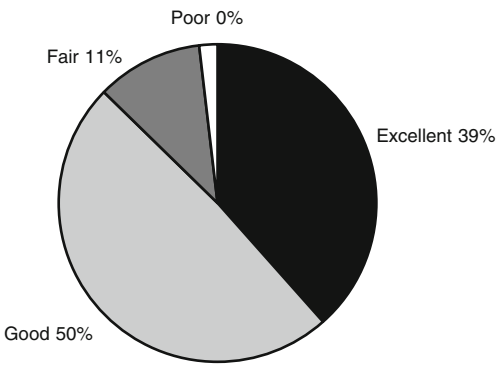

Figure 5 Symptom relief following laparoscopic Heller myotomy was graded by patients with hospital readmissions (n=18) at latest follow-up. *Excellent* Nearly/completely resolved symptoms; *good* greatly improved symptoms; *fair* slightly improved symptoms; *poor* no improvement/worsened symptoms.

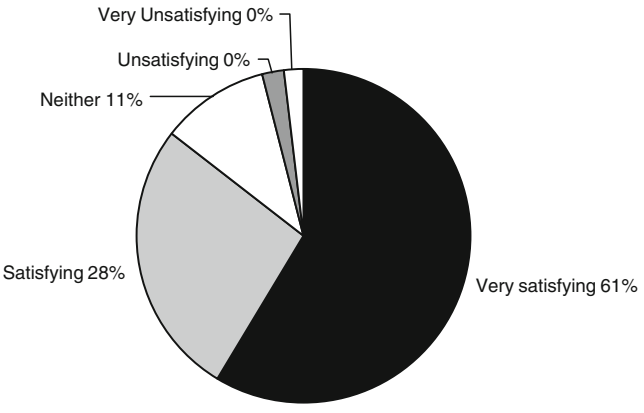

Figure 6 Overall experience of patients that underwent laparoscopic Heller myotomy with hospital readmissions (n=18) reported at latest follow-up. Very satisfying, satisfying, neither satisfying nor unsatisfying, unsatisfying, very unsatisfying.

and whether the patient would have improved with time is debatable. Either way, the patient improved with dilation. These patients ultimately had significant improvement in both the frequency and severity of their symptom scores. Patients readmitted to the hospital were generally troubled by pneumonia, not with symptoms of esophageal obstruction. Two elderly patients, with multiple comorbidities were readmitted for pneumonias, which progressed to empyemas and respiratory failure resulting in their demise. Two other patients who developed postoperative empyemas had significant long-term improvement in both the frequency and severity of their symptom scores after undergoing decortications. Symptom relief is not a surprise with these two patients, as failure to relieve symptoms was not the reason they represented to the ED. Less than 1% of patients were readmitted for symptoms specifically related to preoperative ill health or an operative procedure rather than the disorder (i.e., achalasia) being treated. (e.g., symptoms of obstruction).

Patients with recurrent symptoms are first evaluated for peptic stricture or recurrent nonrelaxing nonstrictured obstruction at the lower esophageal structure (i.e., "recurrent" achalasia). The latter obstruction can result from scarring at the myotomy site, which acts to mimic the original condition for which the myotomy was undertaken. If the cause of dysphagia is due to stricture, antireflux measures (including proton pump inhibitor therapy) are initiated with dilation by tapered bougie (i.e., nonbrusk dilation). If "recurrent" achalasia is identified, brusk dilation can be considered. Risk of perforation at the previous myotomy site discourages most endoscopists from dilation in their setting. Thus, "redo" myotomy seems the best option. If no functional narrowing at the gastroesophageal junction is documented, symptoms may be due to profound esophageal dysmotility, and this should be sought with esophagogram involving food boluses (such as marshmallows, bagel bites,…) in a 15-degree head down position. Pronounced dysmotility causing debilitating symptoms can best be treated by esophagectomy. In our experience, five (1%) of our patients have undergone "redo" laparoscopic Heller myotomies, with their "redo" myotomy often being our first operation on them.[14,20] Dilation after myotomy is common, as they are often undertaken with unclear indications and usually half-heartedly with a single pan of a tapered dilator. In this regard, dilation after myotomy should not necessarily be considered a "failure of myotomy."

A notable number of patients presenting to the ED or requiring hospital readmissions had undergone reoperative or "redo" Heller myotomies as their "index" operation. While reoperative Heller myotomies can and generally do lead to successful outcomes, there is no question that they are more difficult than "first-time" myotomies, and it is more than conceivable that outcomes after "redo" myotomies are less optimal than after "first-time" myotomies.[20] The number of "redo" myotomies in this series of patients presenting to the hospital early after myotomy reflects the difficulties of reoperative myotomy and probably takes some luster off the long-term outcomes experienced by these patients.

In summary, laparoscopic Heller myotomy offers long-term palliation of symptoms of achalasia, regardless of causes or reasons leading to early postoperative ED visits and/or early hospital readmissions, as would be expected, early after myotomy dysphagia, presumably due to edema at the myotomy/fundoplication site. Causes of symptoms or morbidity after myotomy distinct from achalasia (e.g., pain and pneumonia) are more likely related to an operative procedure in general, rather than the underlying disorder (i.e., achalasia) or operation (i.e. Heller myotomy). Notably, causes of ED visits and hospital readmissions do not seem to generally impact long-term outcome. Long-term symptomatic improvement can be and should be expected, even for the very small number of patients that require reintervention for what appears to be inadequate myotomy or fundoplication. Notably, there is a bit of disconnect between relief of symptoms and satisfaction long-term. Symptom relief seems profound and dramatic, while satisfaction seems a bit elusive. Probably, for these patients, satisfaction is negatively impacted by the road traveled to achieve symptom relief. That is understandable. We must focus efforts on postoperative pain relief, identifying patients at risk for postoperative pneumonia, setting early patient expectations, and supporting patients with profound early symptoms and (thankfully uncommon) operative complications. Of the people who have early postoperative emergency room visits and/or hospital readmissions, most will still go on to have good long-term outcomes without further interventions, as edema at the GE junction abates and esophageal emptying improves. The very few patients who require postoperative interventions still report significant palliation of their symptoms relative to before myotomy. In short, despite ED visits and/or hospital readmissions early after myotomy, symptoms of achalasia are well palliated by myotomy long-term.

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J Gastrointest Surg (2008) 12:2133–2140
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Magnetic Augmentation of the Lower Esophageal Sphincter: Results of a Feasibility Clinical Trial

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Received: 21 June 2008 / Accepted: 8 September 2008 / Published online: 10 October 2008

Abstract
Background The high prevalence of gastroesophageal reflux disease continues to encourage the development of treatment modalities to fill the gap between acid-suppression therapy and the laparoscopic Nissen fundoplication. The Magnetic Sphincter Augmentation device has been designed to augment the lower esophageal sphincter barrier using magnetic force. A multi-center feasibility trial was done to evaluate safety and efficacy.
Methods Patients with typical heartburn (at least partially responding to proton-pump inhibitors), abnormal esophageal acid exposure, and normal esophageal peristalsis were enrolled. Patients with hiatal hernia >3 cm were excluded from the study. The device was implanted laparoscopically around the distal esophagus.
Results Over a 1-year period, 38 out of 41 enrolled patients underwent this procedure in 3 hospitals. No operative complications were recorded. A free diet was allowed since post-operative day one, and 97% of patients were discharged within 48 h. The mean follow-up was 209 days (range 12–434 days). The GERD-HRQL score decreased from 26.0 to 1.0 ($p<0.005$). At 3 months post-operatively, 89% of patients were off anti-reflux medications, and 79% of patients had a normal 24-h pH test. All patients preserved the ability to belch. Mild dysphagia occurred in 45% of patients. No migrations or erosions of the device occurred.
Conclusions Laparoscopic implant of the MSA device is safe and well tolerated. It requires minimal surgical dissection and a short learning curve compared to the conventional Nissen fundoplication.

Keywords Gastroesophageal reflux disease · Lower esophageal sphincter · Laparoscopic Nissen fundoplication · Phrenoesophageal ligament · Proton pump inhibitors

Presented at 49th Annual Meeting of the Society for Surgery of the Alimentary tract, San Diego, California, USA, May 20, 2008

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The incidence of gastroesophageal reflux disease (GERD) is increasing along with its complications of Barrett's esophagus and adenocarcinoma.[1–3] This has occurred despite the widespread use of potent acid-suppression therapy, namely the proton-pump inhibitors (PPI). Further, patients on maximum dose PPI therapy may complain of persistent regurgitation or may develop atypical GERD symptoms. The inability of pharmacologic therapy to limit the progression of the disease or to fully suppress all symptoms has encouraged many patients to have anti-reflux surgery, most commonly the Nissen fundoplication. The Nissen procedure, however, is technically complex, it results in major alteration of gastric anatomy, and has variable outcomes from center to center. Consequently, it tends to be applied primarily to patients with advanced reflux disease as an end of the line therapy.

To fill the treatment gap between acid-suppression therapy and the Nissen fundoplication, a variety of endoluminal anti-reflux procedures have emerged. These

endoluminal procedures were primarily designed for use in patients with relatively normal anatomy of the esophagogastric junction (small or no hiatal hernia) and incomplete symptom resolution or non compliance with PPI therapy. Unfortunately, these endoluminal procedures have yet to show consistent normalization of distal esophageal acid exposure as defined by 24-h pH monitoring. Published studies show a pH normalization range of only 25–40%.[4,5] Consequently, a need still exists for a therapy to fill the gap between pharmacologic therapy and the Nissen fundoplication. The Magnetic Sphincter Augmentation (MSA) device was developed to meet this need. The MSA is a laparoscopically implantable device that is designed to restore Lower Esophageal Sphincter (LES) barrier function using magnetic force. The device requires minimal surgical dissection, maintains normal gastroesophageal junction and gastric anatomy, and is designed to preserve physiologic functions such as belch and vomiting. The treatment is currently intended for patients who fail medical therapy but have otherwise normal anatomy of the esophagogastric junction.

The MSA device consists of a series of titanium beads with a magnetic core (Fig. 1). The beads are linked together with independent titanium arms to form a flexible ring that is placed around the distal esophagus. The magnetic attraction of the beads provides a sustained force to augment the LES barrier. The device expands to accommodate a swallowed bolus, and the magnetic force between the beads is exponentially reduced with distension of the sphincter. A multi-center, feasibility trial was done to evaluate the MSA device.

Methods

Trial Objective and Design

The objectives of this prospective, feasibility trial were to: (1) demonstrate the safety of the MSA device; (2) measure the effectiveness of the device in reducing esophageal acid exposure; (3) standardize the laparoscopic technique for implantation of the MSA device; (4) evaluate the effects of the device on the LES and esophageal body function; (5) measure the ability of the device to improve GERD related symptoms and quality of life; (6) measure the ability of the device to reduce GERD related medication use; (7) determine any potential side-effect caused by the device.

Patient inclusion criteria were: typical reflux symptoms at least partially responsive to PPI, abnormal esophageal acid exposure, and normal contraction amplitude and wave form in the esophageal body. Patients exclusion criteria were: younger than 18 and older than 75 years of age, previous upper abdominal surgery, previous endoscopic anti-reflux procedures, greater than 3 cm sliding hiatal hernia, greater than grade A esophagitis according to the Los Angeles classification, and/or the presence of Barrett's esophagus on endoscopic biopsies. The trial design is depicted in Fig. 2.

The study protocol was approved by the Ethical Committee of the IRCCS Policlinico San Donato, University of Milan, Milan, Italy, and the Institutional Review Boards of the Chapman Medical Center, Orange, CA, USA, and Abbott Northwestern Hospital, Minneapolis, USA. Each patient was informed about the investigational nature of the trial, and received detailed information about the

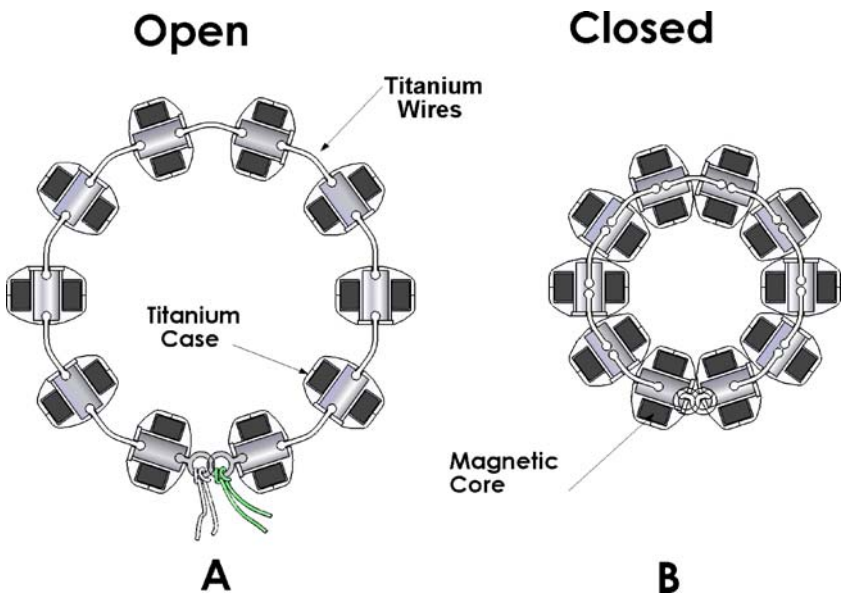

Figure 1 Engineering schematic of the magnetic sphincter augmentation device open (**a**) and closed (**b**). Closed force is 0.40 N and open force is 0.07 N.

Figure 2 Design of the clinical trial.

Screening	Implant	2 week	6 week.	3 month	6 month	12 month	Type of Follow-Up
X						X	Health History
X		X	X	X	X	X	GERD-HRQL
X	X	X	X	X	X	X	PPI, H2, Antacid Use
X				X		X	24hr pH Profile
X				X		X	Manometry/Motility
X				X		X	Endoscopy
X				X		X	Barium Esophagram (Fluoroscopy)
	X		X	X		X	Abdominal/Chest X-ray
	X	X	X	X	X	X	Adverse Events

study protocol. A written informed consent was obtained before enrollment in the trial.

Study Population and Preoperative Assessment

Between February 26, 2007 and May 20, 2008, 41 patients were enrolled for laparoscopic implantation of the MSA device and were evaluated by symptom questionnaire, upper gastrointestinal endoscopy, barium swallow, esophageal manometry, and 24-h esophageal pH monitoring.

The gastroesophageal reflux disease-Health Related Quality of Life (GERD-HRQL) questionnaire was administered pre-operatively and off PPI therapy to all patients prior to any diagnostic test.[6] Upper gastrointestinal endoscopy was performed to assess the presence of esophagitis using the Los Angeles classification. The length of hiatal hernia, if present, was measured as the distance in cm between the Z line and the impression of the crura.

Esophageal manometry was performed and LES pressure and length were measured with a station pull-through technique. The degree of LES relaxation was assessed with five monitored swallows. Esophageal contractility was assessed with ten wet swallows (5 ml each, 30 s apart). Abnormal motility was defined as a mean contraction amplitude of 30 mmHg or less, and/or a greater than 20% prevalence of simultaneous waves.

Twenty-four hour pH monitoring was performed off acid-suppression therapy by placing the pH probe or capsule 5 cm above the upper border of the LES determined by manometry or 6 cm above the Z line determined by endoscopy. Abnormal esophageal acid exposure was defined as a DeMeester pH score >14.7.[7]

Implantation of the MSA Device

The MSA device was supplied sterile and was placed through a 10 mm laparoscopic port. The MSA device was available in different lengths, based on the number of beads, to accommodate the varied esophageal circumferences. Sutures were attached to eyelets at each end of the device to secure the implant. A specially designed sizing tool was wrapped around the distal esophagus before placement of the device, so that the surgeon was able to select the appropriate size of implant (Fig. 3).

The device was implanted laparoscopically under general anesthesia with the patient in the lithotomy position. A 11-mm port for the 30° scope was inserted at the lower third of the distance between the xyphoid process and the umbilicus. An all-purpose 12-mm port was placed in the left subcostal area and a 5 mm dissection port in the right subcostal area in the midclavicular line. An additional 5 mm port was placed below the xyphoid process for liver retraction. A 5 mm port was placed in the left flank at the level of the umbilicus for downward traction of the stomach. With the patient in a reverse (20–30°) Trendelenburg position, the subcardial stomach was retracted downward. The peritoneal reflection anterior to the gastroesophageal junction was divided to expose the esophageal wall. The anterior vagal trunk was identified, but no attempt was made to dissect it from its intramuscular location. The hepatic branch of the anterior vagus nerve was preserved. The lesser omentum beneath the nerve was opened to allow a better exposure of the right crus. The retro-esophageal dissection began along the border of the right crus at the lateral aspect of the distal esophagus, just cephalad to the crural decussation. The posterior vagal trunk was identified. The same dissection was repeated along the left crus of the diaphragm. Gentle dissection from the right opened the retro-esophageal

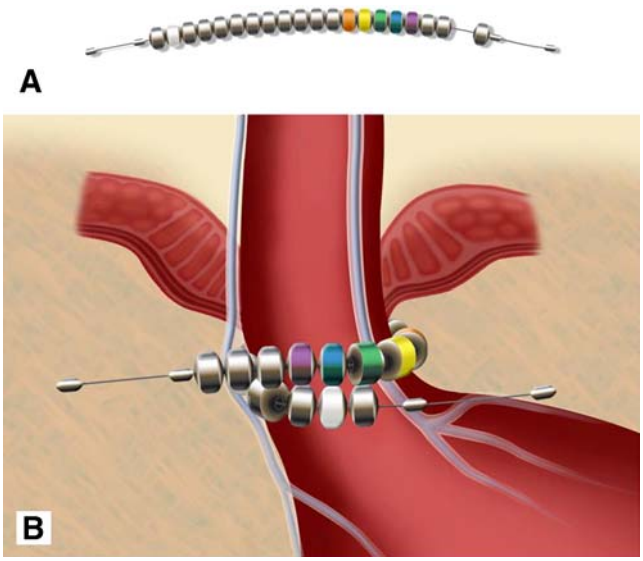

Figure 3 Sizing tool **a** used to fit loosely around distal esophagus **b** to determine the appropriate MSA device for the individual patient.

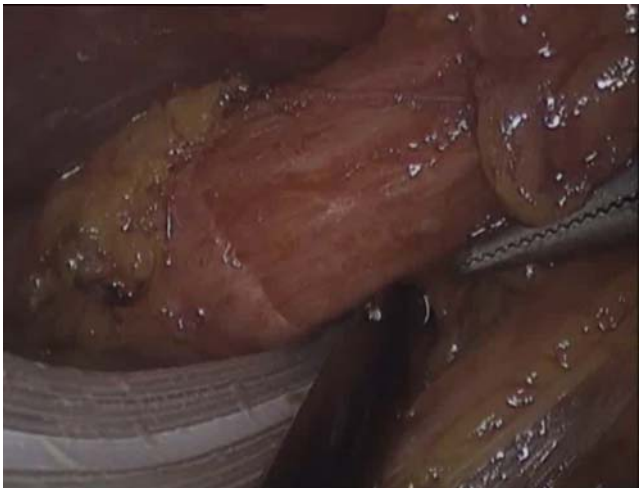

Figure 4 The MSA device is inserted along a tunnel between the esophageal wall and the posterior vagus nerve.

window between the posterior wall of the esophagus and the posterior vagal trunk (Fig. 4). Continuous downward traction on the gastroesophageal junction and application of 10–15 mmHg of positive-end expiratory pressure helped the dissection. A Penrose drain was passed through the retro-esophageal window to encircle the esophagus.

The sizing tool was introduced through the all-purpose trocar, advanced through the posterior esophageal tunnel, and wrapped around the esophagus above the hepatic branch of the anterior vagal trunk. The appropriate size device to be implanted is selected by alignment of the white bead with one of the colored beads (Fig. 3b) The sizing tool was removed and the MSA device inserted. The sutures at both ends of the device were secured with a Ti-Knot ® (LSI Solutions, Victor, NY, USA; Fig. 5).

The target location of the MSA device was the Z line. This location can be verified with intraoperative endoscopy prior to securing the sutures (Fig. 5b). A posterior cruroplasty was added to MSA device placement in five of 38 patients.

Post-operative Assessment

Position and function of the device were evaluated with a standard chest film and a modified barium esophagram the day after the procedure before hospital discharge. The GERD-HRQL questionnaire, upper gastrointestinal endoscopy, modified barium esophagram, esophageal manometry, and 24-h esophageal pH monitoring were obtained at 3 months and 1 year after surgery.

Statistical Analysis

The two-tailed, paired Student *T* test was used to compare pre and post-operative values. Differences were considered significant at the $p<0.05$ level.

Results

Three of the 41 patients enrolled were not implanted with the MSA device. One was converted to a Nissen fundoplication due to the intraoperative finding of a hiatal hernia >3 cm and a leiomyoma at the esophagogastric junction. A second patient withdrew consent before surgery was scheduled; a third patient was ineligible due to preoperative esophageal motility testing results showing ineffective peristalsis. The final study population was composed of 38 patients, 23 males and 15 females ranging in age from 19 to 72 years (median 42.8). The BMI ranged from 19 to 38.4 (median 24.5). All patients complained of heartburn as the primary symptom and were taking PPI (single or double

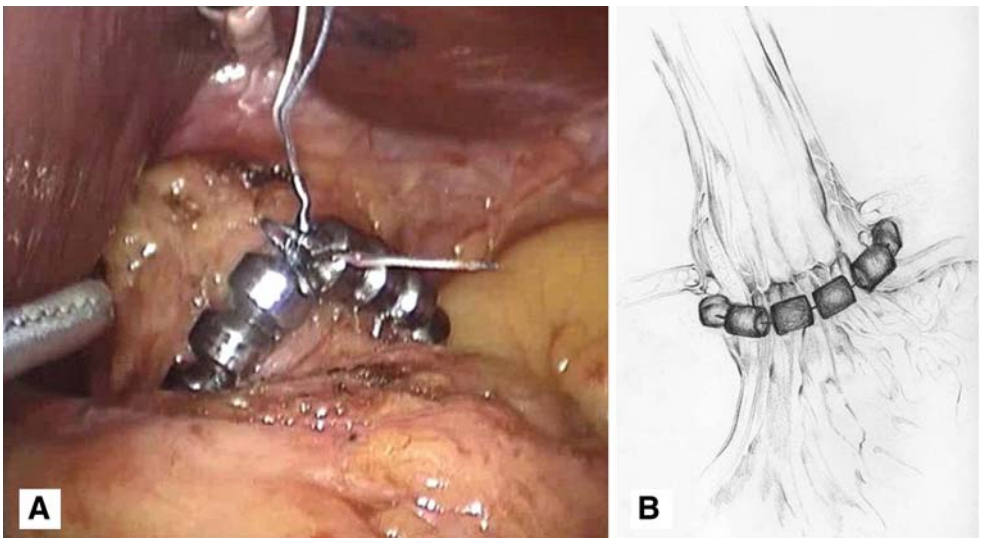

Figure 5 Final intraoperative position of the MSA device (**a**). The target location is the Z line (**b**).

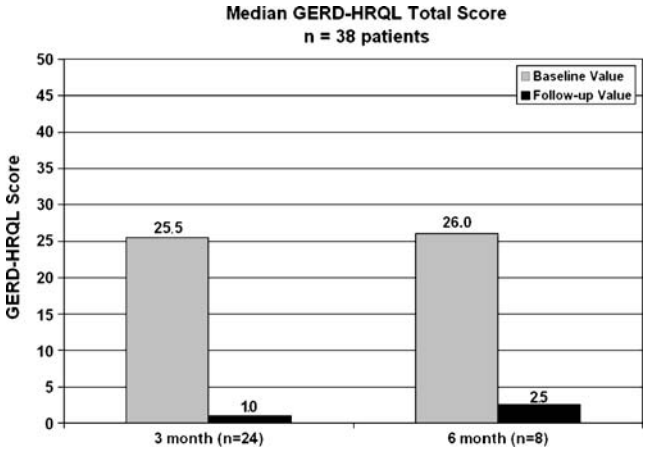

Figure 6 Median GERD-HRQL score before surgery and at various time intervals after surgery.

dose) for acid suppression. A ≤ 3 cm sliding hiatal hernia based on radiologic and/or endoscopic criteria was observed in 60.5% (23/38) of the patients. All patients had an abnormal DeMeester pH score that ranged from 15.1 to 117.3 (median 31.4) after being off acid suppression therapy for a minimum of 10 days.

Post-operative Course

All devices were implanted by the laparoscopic approach without operative complication. The median operative time was 40 min. A regular diet was allowed after radiological assessment of esophageal transit on the first post-operative. All but one patient (37/38) 97% were discharged within 48 h.

Therapeutic Response

As of May 20, 2008 the mean follow-up was 209 days (range 12–434 days). Eighty-nine percent of the patients were off PPI at 3 months. Mild dysphagia occurred in 17 patients (45%) and resolved in the majority without any treatment. One patient required laparoscopic removal eight months after implantation for persistent dysphagia and pathologic esophageal acid exposure on 24-h pH test. The revisional procedure was uneventful, and dysphagia resolved. The median GERD-HRQL score decreased from 26.0 pre-operatively to 1.0 at 3 months and 2.5 at 6 months ($p<0.005$ for both time points) (Fig. 6). A post-hoc questionnaire of was completed by all 38 patients. All reported the ability to belch and, four, the ability to vomit after insertion of the device

Barium Swallow

In 36 of 38 patients the MSA device was observed immediately below the diaphragm (Fig. 7) and in two, 1–2 cm above the diaphragm. Both of the latter patients had a <3 cm hiatal hernia pre-operatively that was not repaired during placement of the device. Both patients normalized their distal acid exposure. No device migration occurred.

Endoscopy

No mucosal breaks occurred. Upper gastrointestinal endoscopy was performed in 24 patients that completed a 3-month follow-up. At endoscopy, the device was 0.5–2.0 cm below the Z line in 19 patients, at the Z line in three, and greater than 2 cm below the Z line in two. Both of the latter patients had pathologic esophageal acid exposure at 3 months testing.

Esophageal Manometry

There were no significant changes in the manometric parameters after MSA implantation compared to pre-surgical manometric data as reported in Table 1.

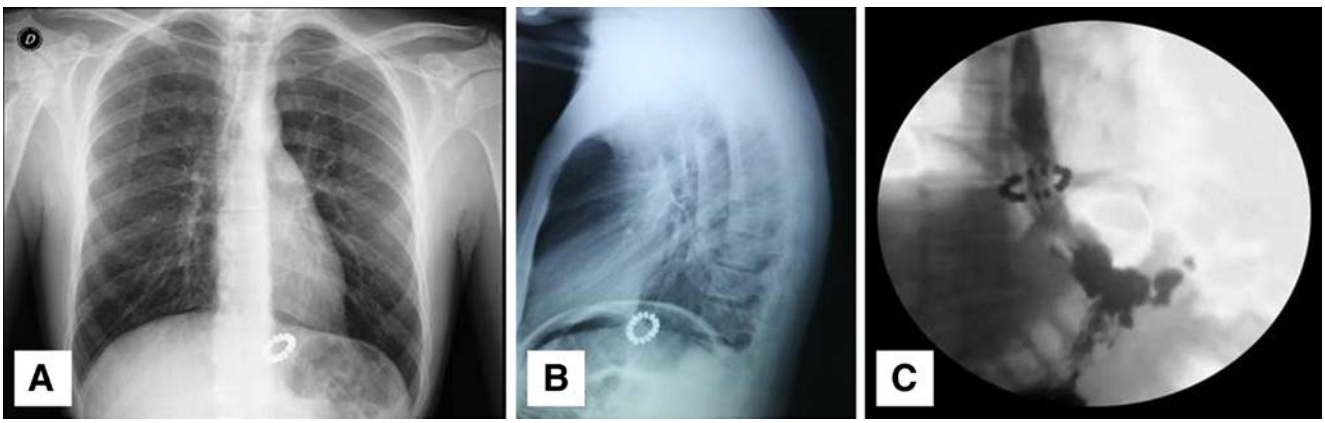

Figure 7 Radiological appearance of the MSA device on AP chest film (**a**), lateral chest film (**b**), and barium esophagram (**c**).

Table 1 Results of Esophageal Manometry Before and After Laparoscopic Implantation of the Magnetic Sphincter Augmentation (MSA) device

	Baseline n=37	Pre n=18	Post n=18	p value
Mean LES resting tone (mmHg)	13.9	14.1	16.0	0.19
Mean LES length (cm)	4.5	4.4	5.3	0.15
Mean LES abdominal length (cm)	2.7	2.7	3.6	0.11
Mean LES relaxation (%)	97	97	98	0.96
Mean swallows effective (%)	96	96	99	0.17

24-hour Esophageal pH Monitoring

Overall, 19/24 (79.2%) patients returned to normal esophageal acid exposure at 3 months. Comparison of the pre- and post-operative pH parameters are reported in Figs. 8 and 9, and in Table 2.

Discussion

Continuous PPI therapy is the first line approach in patients with GERD. However, for a percentage of patients this treatment is insufficient due to incomplete relief of heartburn, persistent regurgitation, drug side-effects, the emergence of atypical symptoms, a desire not to be dependent on life-long pharmacological therapy, and progression of the disease to Barrett's esophagus and adenocarcinoma during treatment. The cumulative effects of these limitations lead many patients with GERD to consider surgical therapy. At present, this is a laparoscopic Nissen fundoplication. It is generally acknowledged that the laparoscopic Nissen fundoplication is a very effective and durable operation when performed in specialized centers.[8–12] However, the success rate varies widely.[13] Reports from the

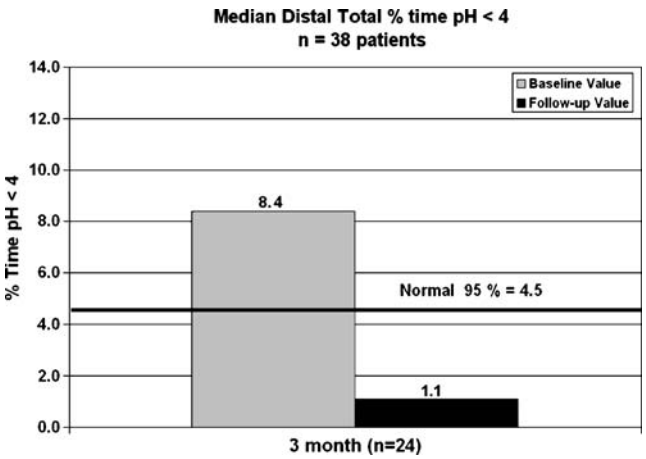

Figure 8 Median distal esophageal acid exposure (% time pH<4) before and after surgery.

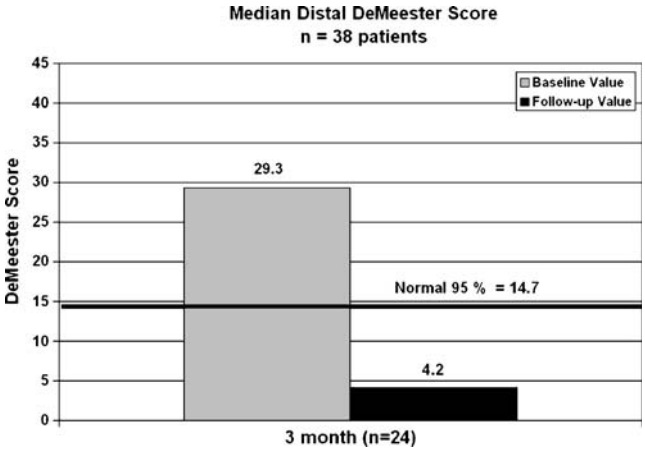

Figure 9 Median composite DeMeester score before and after surgery.

community on Nissen fundoplication outcomes show that only 61% of patients were satisfied with the procedure and 32% were still taking medications on a regular basis for heartburn.[14] This is likely the reason for the reported 30% decrease in the number of anti-reflux operations performed in the USA between 2000 and 2003.[15] The intent of the MSA device is to provide a more simple and standardized minimally invasive surgical therapy for patients with GERD who are dissatisfied with their current medical therapy.

We recognize that a foreign body placed near the gastroesophageal junction can be at risk for erosion into the esophageal lumen. The MSA device has been designed specifically to reduce or eliminate the propensity for erosion. It is nonrestrictive with regard to esophageal motion or distension. The volume of the MSA device is 2 ml or less. This is markedly less than the approximate 50 ml volume of the Angelchik prosthesis and, consequently, the displacement pressure on adjacent tissue is less. Further, at rest, the MSA device is designed to encircle the esophagus in the form of a "Roman arch" to avoid compression of the tubular esophagus. These design features allow the MSA device to work in harmony with the esophagus and lessen the propensity for erosion. In a

Table 2 Results of 24-h Esophageal pH Monitoring Before and After Laparoscopic Implantation of the Magnetic Sphincter Augmentation (MSA) device

	Baseline n=38	Pre n=24	Post n=24	p value
DeMeester score	31.4	29.3	4.2	<0.001
Total % time <pH 4	9.8	8.4	1.1	<0.001
Upright % time <pH 4	10.9	10.6	1.3	<0.001
Supine % time <pH 4	5.0	3.3	0.1	<0.01
No. of episodes	66	67	12	<0.001
No. of episodes >5 min	5.5	5	1	<0.001
Longest episode (min)	31	28	5	<0.04

porcine model, LES augmentation with the MSA device allowed normal eating behavior and weight gain without alteration of tissue histology or erosion of the device.[16]

A legitimate question is why develop a new anti-reflux procedure when a laparoscopic Nissen fundoplication currently exists and has a reputed good outcome. The Nissen fundoplication, when done correctly, is technically complex and results in significant alteration of gastric anatomy. Consequently, it has inconsistent outcomes and a potential for side-effects.[14] This outweighs the benefits for patients with early disease. The ability to perform a simpler and more standardized antireflux procedures in the outpatient setting would make the procedure more acceptable to patients and physicians. At present, the Nissen fundoplication is rarely performed as an outpatient procedure. In contrast, the MSA device is suited for insertion in the outpatient setting. Further, the implantation of the MSA device is expected to be simpler and more standardized, resulting in less outcome variability. We agree that the Nissen fundoplication has a proven track record for patients with advanced GERD and the efficacy of the MSA device for these patients remains to be determined. At present, the MSA device is targeted to fill the treatment gap between patients with failed acid-suppression therapy and those with advanced disease that require a Nissen fundoplication.

This study shows that the implantation of the MSA device requires minimal surgical dissection, thereby preserving the normal anatomy of the stomach and esophagogastric junction. In most patients, a distinct phrenoesophageal ligament was identified and care was taken to preserve the upper leaf of this structure which fuses with the esophageal adventitia.[17] Preservation of the phrenoesophageal ligament, combined with the exclusion of the posterior vagus nerve, is likely to provide a safe anchoring of the MSA device around the LES and to prevent proximal migration. Based on design and supporting in vitro and in vivo testing,[16] the device increases the pressure required to open the LES by interrupting distraction of the sphincter by gastric wall tension. In other words, the magnetic force of the MSA device, which is highest when the device is closed, prevents the LES shortening induced by gastric distension.[18,19] Interestingly, all patients queried in this series were able to belch after surgery. As expected, postoperative manometric values at rest did not change compared to preoperative findings.

This initial clinical experience suggests that laparoscopic placement of the MSA device is a safe and reproducible method of augmenting the LES while preserving the ability to belch and vomit. It has the additional advantage of being a reversible procedure.[20] The MSA device produced consistent symptomatic improvement in all patients and pH normalization in 80% of patients. Further clinical and objective follow-up are underway and an additional trial has been planned to further assess the safety and effectiveness of magnetic sphincter augmentation.

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J Gastrointest Surg (2008) 12:2141–2148
DOI 10.1007/s11605-008-0700-y

Surgical Management of Leiomyosarcoma of the Inferior Vena Cava

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Received: 20 July 2008 / Accepted: 8 September 2008 / Published online: 8 October 2008

Abstract
Introduction Leiomyosarcoma of the inferior vena cava (IVC) is a rare tumor for which en bloc resection offers the only chance of cure. Due to its rarity, however, optimal strategies for the management of the primary tumor and subsequent recurrences are not well defined.
Methods We performed a retrospective review of patients who underwent surgical resection of IVC leiomyosarcoma. We evaluated clinical presentations, operative techniques, patterns of recurrence and survival.
Results From 1990 to 2008, nine patients (four females) were identified. Median age was 55 years (40–76). Presentations included abdominal pain (n=5), back pain (n=2), leg swelling (n=4) and abdominal mass (n=2). Pre-operative imaging studies showed tumor location to be from the right atrium to renal veins (n=1), retrohepatic (n=5), and from hepatic veins to the iliac bifurcations (n=3). En bloc resection included right nephrectomy (n=5), right adrenalectomy (n=4), pancreaticoduodenectomy (n=1), right hepatic trisectionectomy (n=1) and right hemicolectomy (n=1). The IVC was ligated in six patients, and a prosthetic graft was used for IVC reconstruction in three patients. Resection margins were negative in seven cases. Median length of stay was 12 days (range, 6–22 days). Major morbidity included renal failure (n=1) and there was one post-operative mortality. Five patients had leg edema post-operatively, four of whom had IVC ligation. Median survival was 47 months (range, 1–181 months). Four patients had recurrence and the median time to recurrence was 14 months (range, 3–25 months). Two patients underwent successful resection of recurrence.
Conclusions Curative resection of IVC leiomyosarcoma can lead to long-term survival. However, recurrence is common, and effective adjuvant treatments are needed. In selected cases, aggressive surgical treatment of recurrence should be considered.

Keywords Leiomyosarcoma · Inferior vena cava · Resection · Retrohepatic · Surgical resection · IVC leiomyosarcoma · Sarcoma

Presented at the Digestive Disease Week 2008, San Diego, CA, USA, May 2008.

Grant Support: NIH K12 HD 049109 (T.C.G.).

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Introduction

Leiomyosarcoma of the inferior vena cava (IVC) is a rare malignant tumor of the venous system. En bloc resection of the tumor is the only treatment option that can provide long-term survival.[1] However, due to its retroperitoneal location and close proximity to vital structures, careful planning is required before embarking on surgical resection. The most commonly used classification scheme dividing the IVC leiomyosarcoma into upper segment (above hepatic veins), middle segment (between hepatic veins and renal veins) and lower segment (below renal veins) reflects the importance of the major branches of the IVC in dictating operative approach and resectability of the tumor.[1] In addition, management of the IVC after tumor resection is controversial, and primary repair, ligation or reconstruction of the IVC have all been utilized with variable results.

Recurrence occurs in more than half of the patients who undergo curative resection of the IVC leiomyosarcoma.[2] Due to its rarity, however, the optimal strategy for management of recurrences is not well defined, and surgical resection, radiation therapy and systemic chemotherapy have been tried with no clear superior modality. In view of the paucity of data regarding best management of this rare tumor, we sought to evaluate our experience of surgical resection of the IVC leiomyosarcoma with particular emphasis on surgical techniques, management of recurrence and survival outcome.

Method

A retrospective review was performed of patients who underwent surgical resection of the IVC leiomyosarcoma at our institution between November 1990 and May 2008. Institutional Review Board approved the study. Clinical records were reviewed in order to obtain patient demographics, clinical presentation, pre-operative work-up, surgical techniques and morbidity as well as follow-up data on survival, patterns of recurrence and its management. Patients with retroperitoneal leiomyosarcoma originating outside the IVC and invading into the IVC were excluded from the study.

Pre-operative Work Up

All patients underwent contrast-enhanced CT scan of the chest, abdomen, and pelvis to assess resectability of the tumor and to rule out distant metastasis (Fig. 1). In addition, three patients underwent MRI of the abdomen, and three patients underwent caval venogram. Pre-operative CT or MRI scans showed the location of the tumor to be the middle segment of the IVC in five cases, middle and lower segments in three cases and upper and middle segment in one case (Table 1). Proximal extension of tumor thrombus into the right atrium in one patient was confirmed on echocardiogram. One patient had pulmonary embolism at diagnosis and a temporary IVC filter was placed pre-operatively (Fig. 2). Six patients had completely occluded IVC and three patients had partial occlusion of the IVC. All patients had extensive collateral vessels present. No patient had hepatic dysfunction from Budd–Chiari syndrome. Four patients underwent pre-operative biopsy of the tumor, which confirmed the diagnosis.

Operative Technique

Bilateral subcostal incision with upper midline extension was commonly used. First, the superior ligamentous attachments of the liver were taken down to gain access to the suprahepatic IVC and hepatic veins. The right colon was fully mobilized, and a generous Kocher maneuver of the duodenum was then performed all the way to the aorta medially, thus exposing the infrahepatic IVC and both renal veins. The lateral attachment of the hepatic right lobe was incised to expose the retrohepatic IVC. The gastrohepatic ligament was divided and involvement of the caudate lobe by the tumor was assessed. The porta hepatis was routinely encircled with a vessel loop. Short hepatic veins were ligated in order to mobilize the liver from the IVC. This allowed access to the retrocaval region. Dissection was performed in the aortocaval space freeing the aorta from the tumor. Frequently, the tumor was invading the right adrenal gland and/or right kidney, and they were resected en bloc with the tumor (Fig. 3). After clamping the IVC above and below the tumor, hemodynamic changes of the patient were assessed. In one patient, veno-venous bypass was required to maintain venous return to the heart. In one case, tumor thrombus in the right atrium required median sternotomy and cardiopulmonary bypass to remove proximal extension of the tumor before clamping the IVC just below the hepatic vein take-offs. En bloc resection of the tumor required right adrenalectomy, right nephrectomy, right hepatic trisectionectomy, pancreaticoduodenectomy, or right hemicolectomy as needed in order to achieve tumor-free margins.

In all cases, the superior resection margin of the IVC was below the level of the hepatic vein take-off. In six cases, the distal resection margin of the IVC was above the level of the renal veins. In the remaining three patients, it was below the renal veins. In all these three cases, right

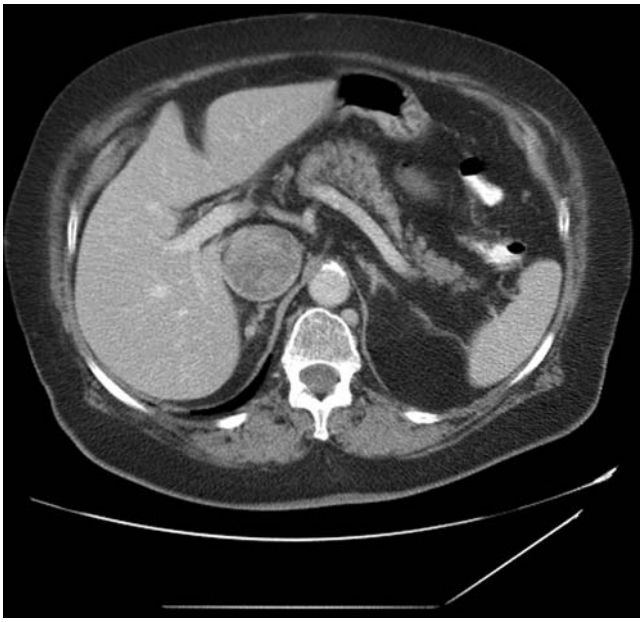

Figure 1 Contrast enhanced CT scan of the abdomen. Intraluminal IVC leiomyosarcoma is visible.

Table 1 Details on Patient Demographics, Presentations, Surgical Techniques and Outcome

Patient	Gender	Age	Symptoms	Location of the tumor	Management of the IVC	EBL (in liter)	En bloc resection	LOS (in days)	Post-op morbidity	Leg Edema
1	M	55	Back pain, leg edema	Middle	Ligation	0.70	None	13	None	No
2	M	40	Abdo pain, leg edema	Middle & lower	Ligation	4.00	R nephrectomy and R adrenalectomy	12	Renal failure, hematoma	Yes
3	F	66	Abdo pain	Middle	20 mm Gore-Tex graft	0.75	R adrenalectomy	6	Atrial fibrillation	No
4	F	42	Abdo mass	Middle & lower	Ligation	0.80	none	6	None	Yes
5	F	76	Abdo pain	Upper & middle	18 mm Dacron graft	0.60	none	15	Atrial fibrillation	Yes
6	M	65	Back pain	Middle & lower	Ligation	10.00	R nephrectomy, R colectomy, pancreaticoduodenectomy	22	death	Yes
7	F	51	Abdo pain	Middle	20 mm Dacron graft	2.50	R trisectionectomy, R nephrectomy, R adrenalectomy	18	Transient hepatic encephalopathy	No
8	M	60	Abdo mass, leg edema	Middle	Ligation	1.00	R nephrectomy, R adrenalrectomy	10	None	No
9	M	53	Abdo pain, leg edema	Middle	Ligation	3.00	R nephrectomy	8	None	yes

nephrectomy was performed, and the left renal vein was ligated in two cases with venous drainage of the left kidney being maintained by collateral vessels. In one case Gore-Tex (polytetrafluoroethylene, PTFE) patch was used to reconstruct the IVC at the junction of the left renal vein.

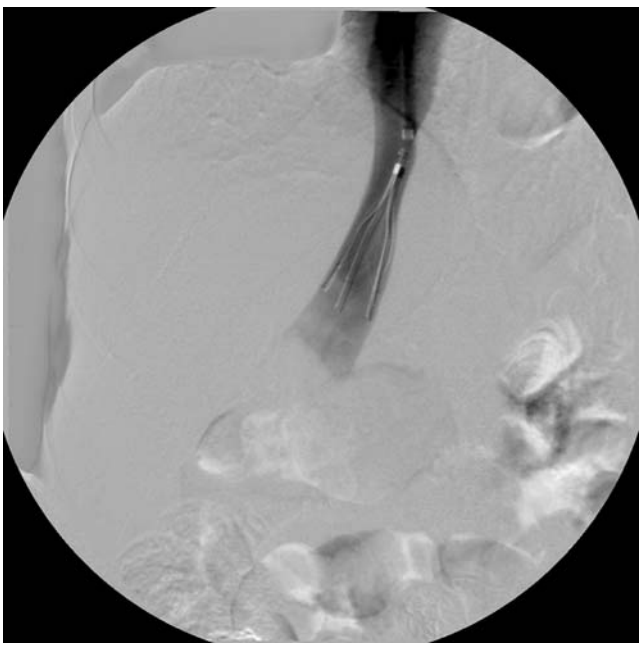

Figure 2 IVC venogram. A temporary IVC is placed above the IVC, which is completely occluded by the tumor.

Management of the IVC after tumor resection was at operating surgeon's discretion. In all cases where a synthetic graft was used, the interposition graft was placed between the infrahepatic IVC and suprarenal IVC in an end-to-end anastomotic fashion (Fig. 4). An omental pedicle was fashioned and was used to cover the synthetic graft and prevent contact with bowel. In the patient with a deep venous thrombosis and/or pulmonary embolism,

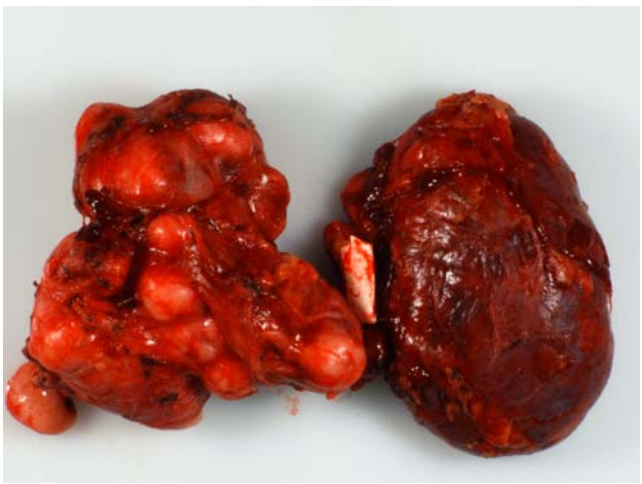

Figure 3 Gross pathology of the IVC leiomyosarcoma (*left*). The right kidney (*right*) was also resected en bloc.

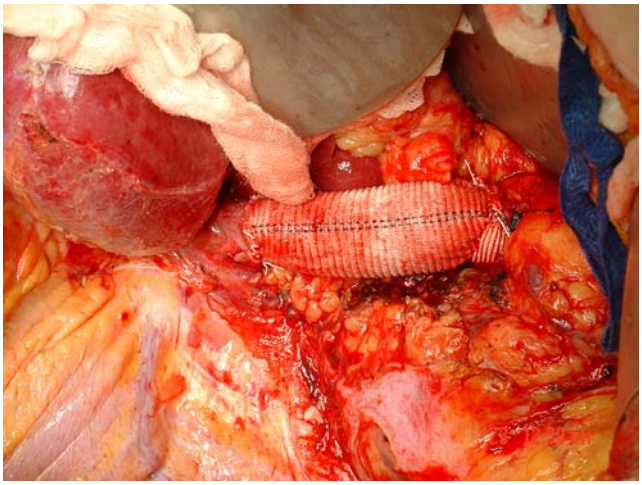

Figure 4 An operative view after the IVC reconstruction with a Dacron graft in an end-to-end anastomotic fashion.

reconstruction was not performed due to the risk of subsequent pulmonary embolism.

Results

Demographics

From November 1990 to May 2008, nine patients (four females) underwent curative resection of IVC leiomyosarcoma. Median age at presentation was 55 years (range, 40–76 years). Demographic and clinical data are shown in Table 1. Presentations included abdominal pain (n=5), back pain (n=2), leg swelling (n=4), and abdominal mass (n=2).

Surgical Procedures and Outcome

Median estimated blood loss was 1 L (range, 0.6–10 L). Median length of stay was 12 days (6–22 days). En bloc resection included right nephrectomy (n=5), right adrenalectomy (n=4), pancreaticoduodenectomy (n=1), right hepatic trisectionectomy (n=1), and right hemicolectomy (n=1; Table 2). The IVC was ligated in six patients, and a prosthetic graft was used for IVC reconstruction in three patients (two Dacron grafts, one Gore-Tex graft).

One post-operative death in our series was from hemorrhagic shock and multi-system organ failure. Major morbidity included one case of renal failure requiring temporary hemodialysis. In addition, there were two cases of atrial fibrillation, one case of retroperitoneal hematoma, and one case of transient hepatic encephalopathy. These complications were medically managed without permanent consequences. Out of six patients who had IVC ligation, four had leg edema after tumor resection, whereas only one out of three patients who had synthetic graft IVC reconstruction developed post-operative leg edema.

Pathology

Median size of the tumor was 10 cm in diameter (range, 6–30 cm; Table 2). Resection margins were negative in seven cases and microscopically positive in two cases. Histologic examination showed that the tumor was high grade in five, moderate grade in three and high/moderate grade in one case. Seven cases had evidence of tumor invading adjacent structures extraluminally.

Follow Up

Median survival from the surgery was 47 months (range, 1–181 months), and six patients were alive at the last follow-up including two patients with recurrence (Table 3). Post-operatively, one patient received adjuvant chemotherapy consisting of five cycles of cyclophosphamide, and doxorubicin therapy, and others were closely observed for recurrence.

Management of Recurrence

Out of eight patients who survived resection of the primary tumor, four were free of recurrence at the last follow-up, and four patients developed recurrence at the median of 14 months from the curative resection (range, 3–25 months). Two patients received systemic chemotherapy for the recurrence. One patient received six cycles of gemcitabine and taxol with subsequent progression, and another patient received two cycles of doxorubicin and ifosfamide and then eight cycles of doxorubicin with progression. Neither exhibited response to systemic chemotherapy.

Two patients developed local recurrence. One underwent right hemihepatectomy to resect local recurrence of segment 7 of the liver 20 months from the initial resection.

Table 2 Pathology of the IVC Leiomyosarcoma

Patient	Size (in cm)	Resection margin	Tumor grade	Extraluminal invasion
1	7.5	R0	II	Absent
2	9.0	R0	III	Present
3	10.0	R0	II/III	Present
4	12.0	R0	II	Present
5	10.0	R1	III	Present
6	22.0	R1	II	Present
7	6.0	R0	III	Present
8	30.0	R0	III	Present
9	11.5	R0	III	Absent

Table 3 Post-operative Treatment, Patterns of Recurrence and Its Management

Patient	Adjuvant Chemotherapy	Time to Recurrence (in month)	Site of Recurrence	Systemic Chemotherapy for Recurrence	Radiation for Recurrence	Surgery for Recurrence	Overall survival (in month)	Status
1	No	20	R hepatic lobe segment 7; suprahepatic IVC; lung and liver	×6 gemcitabine	No	R hepatic lobectomy; ex vivo liver resection & resection of suprahepatic IVC mass; Pulmonary wedge resections & liver RFA	73	Alive
2	No	8	Retroperitoneum, liver, lung	×2 doxorubicin & ifosfamide; x8 doxorubicin	Yes	n/a	52	Alive
3	No	25	Retroperitoneal peri-pancreatic mass	No	Yes	enucleation of the peri-pancreatic mass	47	Dead
4	No	n/a	None	n/a	n/a	n/a	155	Alive
5	No	3	R liver lobe, lung	No	No	n/a	12	Dead
6	No	n/a	None	n/a	n/a	n/a	1	Dead
7	×5 cyclophosphamide & doxorubicin	n/a	None	n/a	n/a	n/a	181	Alive
8	No	n/a	None	n/a	n/a	n/a	8	Alive
9	No	n/a	None	n/a	n/a	n/a	1	Alive

Eight months later, recurrence at the superior resection margin of the IVC was found and the patient underwent ex vivo liver resection to allow resection of the second recurrence near the remaining IVC. At 47 months from the initial surgery and following the two resections of recurrences, the patient was found to have additional lung metastases and liver metastases. He then underwent median sternotomy with pulmonary wedge resections and percutaneous radiofrequency ablation of the liver metastases. The patient went on to receive doxorubicin-based transcatheter arterial chemo-embolization for subsequent liver metastases and systemic therapy with six cycles of trabectedin on protocol. He is currently alive at 73 months from his initial operation with stable disease over the last 6 months. Another patient underwent enucleation of a recurrence at the uncinate process of the pancreas. Two patients received radiation therapy, one after resection of local recurrence, and the other for a local recurrence.

Discussion

Two thirds of patients with leiomyosarcoma of the IVC present with localized disease amenable to curative resection.[1] The International Registry established by Mingoli et al. has helped to clarify natural history of this rare tumor and to identify variables associated with long-term survival.[2] Among several prognostic indicators, surgical resection of the tumor with negative margins is the most important factor that leads to best outcome, with 5-year survival ranging from 33 to 68%.[2–8] The median survival of 47 months in our series supports the view that aggressive resection of IVC leiomyosarcoma with negative margins should be the goal of therapy for those without widespread metastases and who are acceptable operative candidates. We also report that such a resection can be performed with acceptable morbidity and mortality. However, many aspects of IVC leiomyosarcoma present unique challenges for optimal management.

Operative procedures required for tumor extirpation are frequently complex as a result of its retrohepatic location and close proximity to major branches of the IVC. For instance, involvement of the renal vein confluence by the tumor may necessitate nephrectomy, auto-transplantation of the kidney or re-attachment of the tumor-free renal vein stump to the IVC.[9] A 56% rate of nephrectomy in our series confirms the common occurrence of renal parenchymal or vascular involvement by the tumor, and it is consistent with 75% rate reported in the literature.[10] Right nephrectomy is frequently required as a result of short right renal vein stump. The left renal vein, however, can usually be ligated because of its substantial length and adequate venous return maintained by collateral vessels such as gonadal, lumbar and adrenal veins. The locally invasive nature of the tumor also can lead to involvement of other adjacent organs such as the adrenal gland and the liver and an extensive en bloc

resection may be required in an attempt to achieve tumor-free margins.

The location of the tumor in terms of upper, middle, or lower segment of the IVC is another aspect of the tumor that determines operative approach. It is also associated with prognosis as identified in the international registry by Mingoli et al.[2] The middle segment is usually approached by laparotomy and it carries best prognosis after curative resection with 48.3% 5-year survival rate whereas the lower segment tumor is associated with 5-year survival rate of 9.3%.[11] On the other hand, upper segment tumors require a thoraco-abdominal approach or combined median sternotomy and laparotomy. It is frequently inoperable, and the median survival in such cases is reported as 1 month.[11] Therefore, pre-operative determination of the segment of IVC involved by the tumor should be the first step in formulating management strategy. We have found that CT scan of chest, abdomen and pelvis with intravenous contrast was the most informative imaging study for this purpose. Echocardiogram was also useful in assessing intra-atrial extension of the tumor.

In our series, six patients had a completely occluded IVC by the tumor or thrombosis. Impaired venous return by the IVC in such circumstances leads to the development of collateral vessels, and the patency of the IVC is an important variable that guides management of the remaining IVC after tumor resection. Options for IVC reconstruction include placement of a synthetic interposition graft, primary repair, or patch repair of the IVC. The proponents of the ligation technique suggest that extensive development of the collateral vessels obviates the need for IVC reconstruction and that patients with stable renal function in the presence of complete IVC thrombosis tolerate ligation well.[8] In addition, the presence of complete thrombosis below the IVC tumor in the iliac or femoral veins makes post-operative thrombosis of the IVC graft likely as a result of poor inflow, and many consider it a contraindication to the use of graft reconstruction.[12] One must also consider the risk of pulmonary embolism if deep venous thrombosis exists pre-operatively. In support, Hollenbeck et al. noted two cases of peri-operative mortality from pulmonary embolism in the setting of pre-operative IVC thrombosis.[8] In such cases, IVC ligation may be safer.

En bloc resection of the tumor, however, may disrupt pre-existing collateral venous networks and adequacy of the collateral vessels cannot be predicted.[13–15] In addition, the main risks of IVC ligation, namely chronic venous insufficiency of the lower extremities and renal failure from venous obstruction may be ameliorated by IVC reconstruction. In support, we have found that post-operative leg edema was more common in cases where IVC ligation was performed when compared to synthetic graft IVC reconstruction (66% vs. 33%). Due to the small numbers in this study, it is difficult to conclusively state that IVC reconstruction is superior to IVC ligation, but safety and patency of the IVC graft have been documented in the literature in other types of retroperitoneal tumor resection, and it should be considered if no contraindication exists.[15,16]

In addition, post-operative renal failure in our series occurred in one patient who had IVC ligation. Huguet et al. also reported two cases where IVC ligation produced intra-operative anuria and in one case it was associated with renal failure and death.[14] Hardwigsen et al. also reported one case of oliguria after vascular clamping of the IVC and thus required IVC reconstruction.[15] One way to assess the need for IVC reconstruction is measurement of venous pressure in the IVC after clamping. Reconstruction of the IVC may be required if the pressure exceeds 30 mmHg.[7] As for the choice of the IVC graft, a Gore-Tex graft may be preferable to a Dacron graft in that it may better resist changes in intra-abdominal pressure associated with respiration.[6,13] A smaller-diameter graft may also be associated with better patency by maintaining a high rate of blood flow.[13]

Alternatively, primary repair or patch repair of the IVC after resection of the tumor can be performed in select cases.[8] However, due to the locally invasive pattern of growth as well as the tumor's propensity to extend intraluminally, simple excision of the tumor from the IVC and repair of the IVC may lead to high rates of positive margins. Therefore the majority of authors recommend segmental resection of the IVC.[7,17]

Contraindications to surgical resection include the presence of widespread metastases, involvement of major vascular structures such as celiac and superior mesenteric arteries, portal vein and superior mesenteric vein. Although it is not an absolute contraindication, invasion of the aorta by the tumor requires additional major vascular reconstructive procedures, and it should be carefully considered on pre-operative imaging studies.[9,12,18,19] The presence of Budd–Chiari syndrome portends an advanced disease in that the cause of death among the patients reported in the literature with unresectable IVC leiomyosarcoma was Budd–Chiari syndrome in two thirds of cases.[1] Therefore, involvement of the hepatic veins by the tumor is an important variable determining feasibility of curative resection, and its poor prognosis should be kept in mind before offering surgical resection. In rare circumstances, however, IVC leiomyosarcoma causing Budd–Chiari syndrome can be resected using complete hepatic vascular exclusion and re-anastomosis of the hepatic vein stump to the remaining IVC or a synthetic graft.[20]

Recurrence after curative resection of the tumor occurs in approximately 57% of patients, and about a fourth of them are local recurrence only.[2] In our series, recurrence

occurred at a median 14 months. The most common site was the liver and the lungs. Management of recurrence poses a difficult question since there is no standard approach with proven benefit. Radiation has been used in both neo-adjuvant and adjuvant settings, and some believe it may help with local control of disease.[3] Due to the large size of the tumor, however, a wide area needs to be incorporated in the radiation field, and this can be associated with significant damage to adjacent organs. Neo-adjuvant doxorubicin-based chemotherapy has also been used in a small number of patients without proven benefit.[19] Adjuvant chemotherapy based on doxorubicin or combination of doxorubicin and ifosfamide has been shown to prolong time to recurrence and overall survival in other types of sarcoma.[21,22] It may have some benefits in the treatment of IVC leiomyosarcoma, but its rarity makes it difficult to prove efficacy.

Surgical resection of local recurrence or metastasis of the IVC leiomyosarcoma has not been widely reported in the literature (Table 4). The most commonly performed procedure was local excision of retroperitoneal recurrence, followed by lung metastatectomy. We performed resection of recurrences in two patients. One patient is alive at 73 months from the initial operation and after resection of three subsequent recurrences, and the other patient died at 47 months. In view of the fact that aggressive surgical treatment has been utilized with success in some cases of recurrent or metastatic sarcoma,[30,31] surgical resection should be considered in select cases of recurrent IVC leiomyosarcoma. Admittedly, these patients who were eligible to undergo such an aggressive surgery were highly selected, and considerations should be given to other aspects of individual's disease process such as interval and pattern of tumor progression and general condition of the patient.

Conclusion

Long-term survival is possible after curative resection of IVC leiomyosarcoma. Surgical resection can be performed with acceptable morbidity and mortality. A synthetic interposition graft for reconstruction of the IVC is associated with a lower risk of lower extremity edema than IVC ligation, and it should be used in select cases. Recurrence of this rare tumor is common, and resection should be considered in light of the tumor biology and the general condition of the individual patient.

Table 4 Literature Review of IVC Leiomyosarcoma Recurrences Managed by Surgical Resection

Author	Year	Age	Gender	Site of Recurrence	Time to Recurrence	Operation	Chemotherapy	Radiation	Survival	Status
Beiles et al.[23]	1997	44	F	Local	76	Local excision & repair with ePTFE patch	No	No	23	Alive
Cope & Hunt[24]	1954	33	F	Local	16	Local excision, IVC resection, R nephrectomy	No	Yes	29	Alive
Demers et al.[19]	1992	42	F	Local	17	Local excision, transverse colectomy	Yes	Yes	23	Dead
		24	F	Local	30	Local excision, debulking	Yes	No	72	Dead
Dzsinich et al.[25]	1992	48	F	Lung, hip & femur	?	Lung lobectomy	?	?	132	Dead
		74	F	Local	?	Local excision, ePTFE graft	?	?	36	Alive
Ito et al.[4]	2007	60	F	Local	29.5	Local excision, small bowel resection	Yes	No	90.5	Dead
		48	M	Lung	26.4	Lung wedge resection	Yes	Yes	82.5	Dead
		58	F	Local	19.8	Local excision, small bowel resection	Yes	Yes	69.4	Dead
		39	F	Trunk	49.7	Local excision	Yes	Yes	73.9	Alive
Kasano et al.[26]	1995	51	F	Right atrium & local	7	Resection of R atrium tumor thrombus, local excision	No	No	12	Alive
Stuart et al.[27]	1972	58	F	Liver	16	Partial hepatic resection	No	No	35	Dead
Verela-Duran et al.[28]	1979	49	F	Lung	9	Lung wedge resection	No	No	24	Alive
Yuzer et al.[29]	2004	39	M	Local	15	Local excision & Dacron graft	Yes	Yes	?	Alive

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J Gastrointest Surg (2008) 12:2149
DOI 10.1007/s11605-008-0660-2

Optimal Timing of Surgery for Inflammatory Bowel Diseases

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Received: 28 July 2008 / Accepted: 8 August 2008 / Published online: 7 September 2008

Introduction

This introduction was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference on Optimal Timing of Surgery for IBD at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA. The other articles presented in the conference were McLeod RS, Ileal Pouch Anal Anastomosis: Pregnancy—Before, During and After; Rubin DT, An Updated Approach to Dysplasia in IBD; Sands BE, Fulminant Colitis, and Fleshman JW, Pyogenic Complications of Crohn's Disease, Evaluation and Management

Approximately 20% of ulcerative colitis (UC) patients will require surgery at some time during their illness, whereas the number for Crohn's disease (CD) is about 80%. There is little question that the timing of surgical intervention is an important aspect of the care of these patients. The accompanying articles represent a review of some of the key factors that come into play as gastroenterologists and surgeons make the critical judgments of if and when to operate on an inflammatory bowel disease (IBD) patient.

For UC, when surgery is necessary, total proctocolectomy is the operation of choice and provides a permanent cure. Partial colectomy is rarely performed because of the high probability that the disease will recur in the remaining colon. Ileoanal pouch anastomosis (IPAA) has replaced the classic permanent ileostomy as the procedure of choice to accompany a proctocolectomy, although a permanent stoma is a good option in selected patients, especially the elderly.

For CD, surgery is not a cure, but is reserved for certain complications and for times when symptoms do not respond to medical treatment. Using "return of symptoms" as a definition of recurrence after surgery, about 20% of patients show a recurrence after 2 years and up to 80% by 20 years. Recurrence rates seem to be lower when the initial operation is for fibrostenotic disease as opposed to perforating or fistulizing disease.

The decision to perform surgery is a major one, and should be made by weighing all of the key factors for each individual patient. Undoubtedly, many people suffer needlessly because they try to avoid surgery. Surgical delay not only puts the patient through unnecessary periods of pain and suffering; the delay can lead to worse outcomes. On the other hand, it is clear that putting off surgery for a period of time can be of great benefit. In some cases, it may provide time for other treatments to work enough such that surgery becomes unnecessary. Alternatively, the extra time may be used to improve the patient's nutritional status, or get an infection under control, so that the operation can be done with less morbidity.

The accompanying articles address a variety of specific situations that arise in IBD patients, reviewing the issues that come into play as we make the decision to operate. Clearly, as surgeons we need to make these judgments after weighing all of the relevant risks and benefits of immediate versus delayed operation. Ultimately, the goal of optimal timing for surgery is to achieve the best possible outcome for each individual patient.

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J Gastrointest Surg (2008) 12:2150–2152
DOI 10.1007/s11605-008-0671-z

Ileal Pouch Anal Anastomosis: Pregnancy—Before, During and After

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Received: 28 July 2008 / Accepted: 8 August 2008 / Published online: 10 October 2008

Abstract Most females having surgery for ulcerative colitis are young and in the childbearing age years. Quality of life is usually improved following surgery as is sexual function. The improvement is likely related to an improvement in the physical well-being of individuals. On the other hand, recent evidence suggests that surgery has a significant negative effect on the ability of females to conceive, likely due to adhesion formation. Most women who do conceive have few or no problems with the pregnancy. Although some surgeons recommend that women have a caesarian section rather than delivering vaginally to avoid the risk of injury to the anal sphincter, there is little evidence to support this policy. In conclusion, most women can be assured that their overall well-being and sexual function will be improved following surgery for ulcerative colitis but must be counseled that they may experience difficulties conceiving. Strategies to minimize this complication are needed.

Keywords Ileal pouch · Pregnancy · Sexuality · Fertility

Ileal pouch anal anastomosis (IPAA) is the most commonly performed procedure for patients requiring surgery for ulcerative colitis. Patients have embraced this procedure because it eliminates the disease yet preserves the normal route of evacuation. As well, quality of life is excellent in most patients. Unfortunately, though, recent studies have shown that surgery may impact on female sexuality, fertility, pregnancy, and delivery which are important issues given that most patients having surgery are young and in their child-bearing years.

This paper was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference on Optimal Timing of Surgery for IBD at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA, USA. The other articles presented in the conference were Hodin RA, Introduction: Optimal Timing of Surgery for Inflammatory Bowel Diseases; Rubin DT, An Updated Approach to Dysplasia in IBD; Sands BE, Fulminant Colitis; and Fleshman JW, Pyogenic Complications of Crohn's Disease, Evaluation and Management.

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Sexuality

After IPAA, most women experience no change or an improvement in overall sexual activity and enjoyment. In a recent prospective study by Davies et al., 73% of females had abnormal pre-operative sexual function scores based on a validated instrument, FSFI, used to assess female sexual function.[1] Postoperatively, there was a significant improvement with only 25% having abnormal scores 12 months following surgery. Improved overall physical well-being after surgery has been suggested as the reason for the improvement. On the other hand, dyspareunia, vaginal dryness, and incontinence have been reported in a small proportion of women post-operatively.

Infertility

Many women who have had IPAA have not started or completed their family. Studies have reported that approximately 45% of women attempt to become pregnant following surgery.[2–3] Using different measures of reproductive ability, research has consistently demonstrated that IPAA is associated with a significant decrease in female fertility.[2–4] A Scandinavian study was the first to show that there was a significant decrease in the expected number of births in women having IPAA and furthermore, that 29% of women who did conceive required in vitro fertilization.[5] This same group showed that fecundability, which is the biological ability to become pregnant per month of unprotected intercourse, among women with ulcerative colitis was similar to the general population prior to surgery but decreased following IPAA.[6] The cumulative incidence of pregnancy was only 36% in women who tried to become pregnant following IPAA whereas 88% of women in the general population and 90% of women with ulcerative colitis who had not had surgery were successful in becoming pregnant. Johnson et al. reported infertility rates in women with ulcerative colitis pre- and post-operatively and compared them to the reported rates in the Canadian population.[3] In this study, infertility was defined as failure to become pregnant after 12 months of unprotected intercourse while married or cohabitating, and between the ages of 18 and 44 years of age. Infertility was reported in 36.8% of women who had had surgery compared to a rate of 13.3% in women who had not undergone surgery. These rates can be compared to published infertility rates in the normal North American population of 8.5–10.2%. They also reported that 97% of women who attempted to become pregnant prior to the diagnosis of ulcerative colitis were successful; 98% were successful after the diagnosis of ulcerative colitis was made, but only 56% were successful following IPAA. Finally, the use of fertility treatments was significantly higher in the post-surgery cohort compared to those who had not had surgery (30.3% vs. 3.3%).

It is postulated that the infertility problems are likely due to adhesion formation following surgery and in particular, pelvic dissection. This hypothesis is supported by a study which showed that women with familial polyposis who had a colectomy and ileorectal anastomosis rather than IPAA did not have a decreased fertility rate.[7] Another study showed an alteration in pelvic anatomy following proctectomy as well as following IPAA supporting the hypothesis that the problem may be due to the pelvic dissection.[8]

Given the impact of IPAA on female reproductive ability, women must be preoperatively counseled regarding this risk. Although infertility may be increased following IPAA, deferring surgery until a woman has completed her family is unlikely to be a feasible option. Women who are referred for surgery typically have active disease that has become refractory to medical management.

For women with active disease who require surgery, one consideration is to perform a colectomy with end ileostomy and defer IPAA since previous studies have shown that colectomy alone does not decrease fertility. While this may be acceptable to some patients, having a stoma for a prolonged period of time is unlikely to appeal to most women. Having a stoma in a young woman might negatively impact on her perception of body image and prevent some from developing intimate relationships. Other strategies such as oophoropexy and the use of anti-adhesion substances in the pelvis have been proposed but to date there are no data to prove the safety or effectiveness of these interventions. Some have also suggested that laparoscopic IPAA may decrease the risk of infertility because laparoscopic procedures tend to decrease adhesion formation but again this is unproven.

Pregnancy and Delivery

While conceiving may pose a problem, most studies have shown that pregnancy following IPAA is safe and not associated with increased maternal or fetal morbidity or mortality.[9, 10] Furthermore there appears to be no increase in pouch-related complications or bowel obstruction during pregnancy. The concern is whether vaginal delivery should be recommended. Because of stool generally being less formed in individuals with a IPAA, any degree of anal sphincter injury may lead to deterioration of functional results and in particular, incontinence. For this reason, many colorectal surgeons and obstetricians have recommended that women with a IPAA have a planned cesarean section. This is reflected by cesarean section rates of 38–78% after IPAA which are considerably higher than the North American average of 22%. There are multiple retrospective studies but no reported data to suggest that the risk of an anal sphincter tear is increased. Some women do experience transient worsening of their functional results during pregnancy, but there are no long-term differences in functional outcomes between patients who have had a vaginal delivery compared with a cesarean section. Furthermore, there are data to suggest that women who have a pregnancy and vaginal delivery following IPAA have similar long-term function compared to women who did not have a pregnancy following IPAA. The difficulty with these data is that the series are small and therefore the true rate of sphincter injury in this group is uncertain. The counter argument to planned cesarean section is that the morbidity to both the mother and fetus is generally higher than with a vaginal delivery.

Conclusion

In conclusion, while IPAA may have a negative impact on sexuality, fertility, pregnancy, and delivery in some women, outcomes and overall quality of life after surgery are generally excellent. Given the young age of most patients at the time of IPAA, women need to be fully aware of the alternatives and associated risks. Further research, particularly in the areas of fertility and delivery, is needed to help us better understand the etiology of these problems and their magnitude, and to develop strategies to minimize complications.

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J Gastrointest Surg (2008) 12:2153–2156
DOI 10.1007/s11605-008-0672-y

An Updated Approach to Dysplasia in IBD

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Received: 28 July 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Introduction Long-standing inflammation of the colorectum in ulcerative colitis (UC) and Crohn's disease (CD) has been associated with an increased risk of subsequent dysplasia and colorectal cancer. Historically, it was described that the neoplastic transformation in these inflammatory bowel diseases (IBDs) occurred via a different biologic pathway and not by the non-IBD polyp-cancer pathway and predictable lag time of progression. Therefore, prevention strategies have focused on the detection of dysplasia in flat mucosa, and existing guidelines have recommended performance of interval surveillance colonoscopies with random biopsies to identify such lesions with proctocolectomy when they are confirmed.
Discussion The use of a new technology higher-resolution colonoscopies has led to the appreciation more recently that dysplasia in IBD may be visible with standard optical colonoscopy and can be identified in an even more sensitive manner using chromoendoscopy. Furthermore, emerging evidence favors the intuitive understanding that neoplastic transformation in IBD is linked to the degree of inflammation and that disease control may therefore modify this risk and its subsequent prevention approaches.
Conclusion Future IBD cancer prevention strategies and timing of surgery in at-risk patients will require a better understanding of this evolving field.

Keywords Dysplasia · Colorectal cancer · Inflammatory bowel disease · Chemoprevention · Aminosalicylate therapy · Chromoendoscopy

It has been historically accepted that there is an increased risk of colorectal cancer (CRC) in patients with chronic ulcerative colitis (UC) and probably a similar risk in patients with Crohn's disease (CD) of the colon.[1,2] However, more recent reports have suggested that this risk may have been effectively reduced, possibly because of effective surgical procedures for medical refractory patients, access to disease-controlling therapies, and effective prevention programs.[3–5] Although prospective prevention trials do not exist, consensus guidelines support enrollment of UC patients (and probably CD patients) in cancer prevention programs that are primarily focused on secondary prevention.[6,7] Secondary prevention of CRC in chronic colitis requires screening and surveillance colonoscopic examinations with the intention of identifying early stage cancer or precancerous dysplasia and a plan of action (surgery) when these lesions are found.

When identified by an experienced pathologist, dysplasia is an unequivocal neoplastic change in the epithelium. In the standard nomenclature, it should be characterized as high grade, low grade, or indefinite (favor positive or favor negative).[8] Although the natural history of dysplasia in IBD is not fully appreciated, we do know that dysplasia is associated with risks of synchronous dysplasia and concur-

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Table 1 Retrospective Studies of Dysplasia Visibility Using White Light Optical Colonoscopy

	St. Mark's Group, London[15]	University of Chicago[16]
Years studied	1988–2002	1994–2004
# of patients	525	622
# of surveillance exams	2,204	1,339
# of neoplastic areas (# of patients)	110 (56)	73 (46)
Per lesion sensitivity	77.3%	61.6%
Per patient sensitivity	89.3%	78.3%

rent adenocarcinoma.[9,10] High-grade dysplasia has been associated with concurrent adenocarcinoma in 45–67% of colectomy specimens and therefore demands immediate proctocolectomy. Low-grade dysplasia has been associated with concurrent adenocarcinoma in 19% of colectomy specimens in several studies, and in general, it was confirmed that low-grade dysplasia, even in one biopsy, should prompt discussion of colectomy.[3,11] In one retrospective review of patients with low-grade dysplasia who did not go immediately to colectomy, there was progression to higher grades of neoplasia (high-grade dysplasia or adenocarcinoma) in a predicted 53% of the patients over 5 years.[10] Therefore, at the current time, it is my practice to recommend surgery for my patients with confirmed low-grade dysplasia in flat mucosa on even one biopsy. However, there remains an ongoing debate about whether certain patients with low-grade dysplasia can instead be followed *with a more intensive* surveillance protocol, but this is not uniform in its definition, evidence, or approach.

There are some similarities and important differences in the neoplastic progression of patients with chronic inflammatory bowel disease (IBD) compared to the sporadic and hereditary CRC in non-IBD patients. Neoplastic change in IBD appears to occur via a number of specifically defined risk factors, including longer duration of disease, greater extent of colorectal involvement, greater degree of histologic inflammation, family history of CRC (independent of family history of IBD), and primary sclerosing cholangitis. Importantly, the biology of dysplasia in IBD is different than that in the sporadic adenomatous polyp. IBD patients develop precancerous dysplasia in association with CRC, but this is not in the more visible (and discreetly resectable) polypoid lesions, but rather in flat mucosa that had been previously termed "invisible" dysplasia, because of the difficulty in identifying it using barium radiographs and early technology fiberoptic colonoscopes. Therefore, guidelines were developed that promoted a systematic random sampling of the colonic mucosa with biopsies throughout the colon at regular intervals.

The current approach to detection of dysplasia relies on optical colonoscopy with a screening examination after 8 years of disease and surveillance examinations every 1–2 years subsequently.[7,12,13] An important exception to this approach is for patients with primary sclerosing cholangitis (PSC), who should have surveillance exams immediately at diagnosis of PSC and yearly thereafter. Traditional teaching has emphasized that dysplasia in colitis is often "invisible" or in flat mucosa and, therefore, only detected in a systematized sampling approach to the surface area of the colon using random biopsies (at least 33 biopsies obtained as four-quadrant biopsies every 10 cm). More recently, at least two studies have confirmed that the so-called "invisible" dysplasia is actually visible with standard technology and white light examinations as mucosal irregularities, polypoid lesions or

Table 2 Studies of Chromoendoscopy for Dysplasia in UC Consistently Demonstrate Improved Sensitivity for Detection of Dysplasia

Author (Year)	Institution	# of UC Patients	Type of Imaging	Results	
				# of dysplastic Lesions (chromo vs. conventional)	Sensitivity/ specificity
Kiesslich (2003) [17]	University of Mainz, Germany	263	Methylene blue	42 (32 vs. 10)	93% sensitivity 93% specificity
Rutter (2004) [15]	St. Mark's Hospital, Harrow, UK	100	Indigo carmine	7 (7 vs. 0)	Not given
Hurlstone (2005) [18]	The Royal Hallamshire Hospital, Sheffield, UK	350	Indigo carmine and magnification	93 (69 vs. 24)	93% sensitivity 88% specificity
Kiesslich (2007) [19]	University of Mainz, Germany	161	Confocal endomicroscopy	23 (19 vs. 4)	94.7% sensitivity 98.3% specificity 97.8% accuracy
Dekker (2007) [20]	Academic Medical Center, Amsterdam, The Netherlands	42	Narrow-band imaging	15 (8 vs. 7)	Not given

What remains unclear is whether these lesions have the same predictive value or outcomes as previously defined dysplastic lesions in colitis

masses, challenging this long-held belief.[14,15] This is further supported by the emerging understanding that dye-spraying or digital filtering technologies can be used to enhance visualization of abnormal surface architecture and identify dysplasia more accurately than a random or targeted approach with white light. Adding magnification or confocal microscopy improves the ability to detect dysplasia even further (Table 1).[16–20]

At the current time, although some experts advocate the use of dye spraying with methylene blue or indigo carmine routinely, this has yet to be adopted as a standard of care or incorporated into our guidelines, and important issues remain unresolved, such as how to train our colleagues in this approach, what the outcomes of patients who have dysplasia identified this way may be, and whether this is a cost-effective strategy.

For UC, when surgery is performed for neoplasia, because of the diffuse organ involvement and, therefore, the nature of the at-risk colonic epithelium, there is little debate that the recommended surgery is a proctocolectomy, with or without a restorative ileoanal pouch procedure. The surgical approach should follow the standard surgical oncology technique including lymph node dissection. Many IBD surgeons advocate a hand-sewn ileoanal anastomosis with a mucosectomy instead of a stapled anastomosis based on the idea that any island of epithelium left in vivo with stapled anastomoses may eventually harbor dysplasia or cancer. This has not been proven, however.

The approach to adenocarcinoma in CD of the colon is much less uniform, and it remains unclear whether the patient should have a partial resection consistent with the usual surgery for non-IBD CRC or have a more extensive resection or even total proctocolectomy with end ileostomy. The extent of colonic involvement in CD as well as additional factors such as perianal or small bowel disease may influence the choice of surgery in these situations.

Polypoid dysplasia in IBD is a more difficult challenge than flat (previously termed “invisible”) dysplasia. Polypoid dysplasia is currently defined as an endoscopically discreet lesion that can be removed in its entirety using a standard polypectomy technique (snare or forceps with cauterization). Current studies (with 3–4 years’ follow-up) suggest that a discreet dysplastic polypoid lesion in the setting of colitis can be removed and, *in the absence of dysplasia in flat mucosa* elsewhere, the patient followed with a more intensive surveillance program. This terminology and approach must be distinguished from the patient with a dysplasia-associated lesion or mass (DALM), defined (now) as an endoscopically unresectable lesion, usually one with irregular borders or a flat, spreading appearance. The finding of DALMs should prompt proctocolectomy given their association with synchronous lesions and concurrent adenocarcinoma (Table 2).[15,17–20]

Although dysplasia or cancer of ileoanal pouches has been reported, this remains an area of little data, and therefore, surveillance of pouches in patients with or without previous dysplasia is not well defined. Limited case series from referral centers have suggested that neoplasia in the rectum of the precolectomy patient may put patients at increased risk for recurrence in the pouch, but this has been questioned in some recent reviews.[25]

In summary, our current approach to CRC prevention in IBD is based on the use of screening and interval surveillance colonoscopies with random and targeted biopsies to identify dysplasia or cancer in chronically inflamed colonic mucosa. The detection, diagnosis, and decision analysis is difficult, but remains of reasonable rationale and, at the current time, is the standard of care in these at-risk patients. In the near future, it is expected that stratification of prevention strategies may be based on the degree of inflammation and disease control. In addition, we anticipate that the future incorporation of improved optical techniques and a greater understanding of the natural history of dysplasia will result in a modified approach to cancer prevention in these patients.

Conflicts of interest I have received consulting fees and grant support from Procter and Gamble Pharmaceuticals and Salix Pharmaceuticals.

I have received consulting fees from Axcan Pharma and Shire USA.

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J Gastrointest Surg (2008) 12:2157–2159
DOI 10.1007/s11605-008-0661-1

Fulminant Colitis

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Received: 28 July 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract Fulminant colitis is an important clinical challenge despite great progress in its management over the decades. Corticosteroids greatly reduced mortality and colectomy rates, however, case fatality rates remain at roughly 2%. The goal of medical therapy is to prevent colectomy while avoiding complications that may lead to death or worsen the outcome of colectomy, if this cannot be avoided. In addition to corticosteroids, cyclosporine and infliximab have been used in the setting of severe colitis. Rescue therapy with cyclosporine must be followed by maintenance therapy with a thiopurine agent if successful remission is to be maintained durably. Rescue therapy with infliximab may be followed by maintenance therapy with the same agent, or in some cases, by a thiopurine agent. Both cyclosporine and infliximab may be associated with increased risks, such as neurotoxicity in the case of cyclosporine, or opportunistic or serious infection in the setting of immune suppression from either agent. In either case, it is critical to avoid excessive prolongation of unsuccessful medical therapy if optimal surgical outcomes are to be achieved. A great deal of judgment is needed to guide the timing of colectomy, but it is clear that mortality increases as the time to colectomy is prolonged.

Keywords Fulminant colitis · Inflammatory bowel disease · Crohn's disease · Infliximab · Ulcerative colitis

Fulminant colitis presents a significant threat of mortality, and requires a coordinated effort of surgeon and gastroenterologist to achieve the best possible outcome. It is difficult to apply a precise definition to the term fulminant colitis, but it generally consists of the most severe form of colitis and is part of the spectrum of disease that has been called acute severe colitis. Historically, the case fatality rate of acute severe colitis diminished with the introduction of corticosteroids in the 1950s from 30% to less than 2%, while colectomy rates have been expected to occur among one-third of patients within 6 weeks of initiating therapy.[1,2] The goal of medical therapy has been to reduce the need for colectomy while avoiding fatal complications.

Fulminant colitis may occur as the initial presentation of de novo idiopathic inflammatory bowel disease (IBD), or in patients with well-established disease. De novo presentations present a particular diagnostic challenge. It is not always possible to distinguish among severe presentations of infectious colitidies, ischemic colitis, and a new presentation of Crohn's colitis or ulcerative colitis. Careful evaluation should include stool culture and sensitivity, ova and parasites, *Clostridium difficile* toxin or culture, and colonic biopsy to exclude cytomegalovirus.[3] If the onset of disease is very recent, changes of chronicity may not be present on colonic histopathology; however, on close questioning, many patients will concede mild symptoms preceding their acute exacerbation and evidence of chronic

This paper was originally presented as part of the SSAT/AGA/ASGE State-of-the-Art Conference on Optimal Timing of Surgery for IBD at the SSAT 49th Annual Meeting, May 2008, in San Diego, CA, USA. The other articles presented in the conference were Hodin RA, Introduction: Optimal Timing of Surgery for Inflammatory Bowel Diseases; McLeod RS, Ileal Pouch Anal Anastomosis: Pregnancy—Before, During and After; Rubin DT, An Updated Approach to Dysplasia in IBD; and Fleshman JW, Pyogenic Complications of Crohn's Disease, Evaluation and Management.

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inflammation and altered architecture may be found. Even after gross and microscopic examination of the resected colon the presence of deep ulceration and transmural inflammation may be present in Crohn's disease, as well as ulcerative colitis. Few differences exist between the medical therapies shown to be effective in these two diseases; therefore, the need to distinguish between them relates mainly to the appropriate choice of surgical procedure.

Clinical criteria for a severe attack of ulcerative colitis were proposed by Truelove and Witts to consist of ≥6 diarrheal stools per 24 h, the presence of one or more of the following signs: obvious blood in the stool, fever (temperature greater than 100.0°F), pulse ≥90, hemoglobin ≤10.5 g/L, and erythrocyte sedimentation rate >30 mm/h.[2] The endoscopic appearance is a valuable addition, as many patients with clinical symptoms of moderately severe colitis will be found to have endoscopically severe disease, with important implications for outcome.[4] Cautious lower endoscopy has been shown to be safe in the setting of severe colitis when cautious advancement and insufflation are done.[4–7]

In addition to providing diagnostic information, endoscopy can assist in prognostication. Deep ulcerations bear a poor prognosis for response to medical therapy,[6] as do a finding of mucosal islands seen on plain abdominal radiograph.[8,9] These represent ulcerations penetrating to the muscularis and suggest that the disease is unlikely to respond to medical therapy. Plain abdominal films may also supplement serial abdominal examinations to detect toxic megacolon, a finding that necessitates urgent surgery. The presence of mucosal islands or a colonic diameter of >5.5 cm is associated with colectomy in three out four patients.[10] A finding of colonic wall thickening does not help to differentiate ulcerative colitis from Crohn's colitis in the midst of a severe flare.

Intravenous corticosteroids are generally the first-line treatment for severe colitis. Doses in excess of hydrocortisone 100 mg IV four times daily or methylprednisolone 60 mg IV daily do not have superior efficacy.[11] In addition, continuous infusion of corticosteroids is not more efficacious than bolus dosing.[12] Unfortunately, no more than 60% of patients with severe colitis treated with intravenous corticosteroids respond fully. After 3 days of high dose intravenous corticosteroids, 85% of patients with more than eight stools per day and a C-reactive protein greater than 45 mg/l were found to require a colectomy during that admission.[13] Another study suggested that after 24 h of intravenous corticosteroids albumin <30 g/l or pulse >90 were associated with a 62% failure rate.[10] The value of these predictive factors is that they facilitate planning for rescue therapy with other agents and for surgery.

Rescue therapy with cyclosporine for patients' refractory to intravenous corticosteroids has been helpful in decreasing the need for short-term colectomy.[14] Transition to maintenance with 6-mercaptopurine or azathioprine further decreases the long-term risk of colectomy.[15] However, cyclosporine is associated with significant short and long-term toxicities, including neurotoxicity and risk of seizure in patients with low serum cholesterol or magnesium, and infection, including with *Pneumocystis*. Infliximab has also been used with some success in patients with moderate to severe disease, and does appear to decrease the rate of colectomy at 3 months.[16] Direct randomized comparison of the efficacy and safety of infliximab and cyclosporine has not been performed, raising questions about which should be the treatment of choice. Limited data suggests that sequential use of cyclosporine and infliximab, or vice versa, in patients with severe colitis is not effective and bears prohibitive toxicity and mortality.[17] Patients who fail either therapy should submit to colectomy as soon as possible to avoid further deterioration in their overall condition. An additional controversy, however, arises from reports of increased risk of complications among patients undergoing surgery after exposure to infliximab.[18]

An important pitfall in the care of patients with severe colitis is waiting too long with hopeful expectations of response, whereas it is apparent that when surgery is delayed there is a higher risk of morbidity and mortality. Patients admitted urgently for a UC flare whose surgery is performed more than 6 days after admission have an adjusted odds ratio of in-hospital mortality that is ~2 compared to those who have an earlier surgery.[19] Therefore, most patients admitted with a severe flare of UC, and all admitted with fulminant colitis, should have the benefit of early consultation from a surgeon.

Optimal care of patients with severe colitis continues to involve a great deal of judgment. Avoiding mortality must remain the guiding principle of care, while recognizing that some patients may safely maintain the integrity of their colon through appropriate and conservative medical care, with daily reappraisal of the patient's condition.

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J Gastrointest Surg (2008) 12:2160–2163
DOI 10.1007/s11605-008-0673-x

Pyogenic Complications of Crohn's Disease, Evaluation, and Management

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Received: 28 July 2008 / Accepted: 8 August 2008 / Published online: 23 September 2008

Abstract The principal by which treatment of pyogenic complications anorectal disease is guided should rely heavily on small procedure with medical management of rectal disease and limitation of proctectomy. Management of pyogenic complications of abdominal Crohn's by an elective approach after percutanea drainage of abscess and nutritional repletion should prevent long term complication even when its patient is receiving immune suppressive therapy.

Keywords Crohn's disease · Infliximab · Fistula · Percutaneous draining · Timing of operation

Patients with Crohn's disease are prone to developing pyogenic complications: most common in the perianal area or intra-abdominal abscesses and/or fistulas. Each of these is managed differently, and the timing of definitive operation is influenced by the management of the acute pyogenic complication to achieve an elective or nonacute condition. This manuscript will look at the methods of obtaining control of the pyogenic complication and the timing of the subsequent definitive procedure.

Perianal abscess and fistula occur in 60% to 80% of patients with Crohn's disease.[1] The perianal Crohn's Disease Activity Index (PCDAI) is used to quantitate the effect of the perianal disease and allows evaluation and subsequent follow-up to monitor treatment in these individuals. The evaluation of patient's with perianal Crohn's disease includes clinical, operative, and imaging techniques. Clinical observation of the perineum is the basis of the PCDAI. However, imaging techniques may better define the fistulizing disease. Detection of fistula tracts using endorectal ultrasound can be improved with computer analysis. Approximately 64% of patients can be accurately staged with this modality.[2] Magnetic resonance imaging is less user dependent and yields an accuracy of 88%.[2] Endorectal ultrasound allows treatment to be based on "radiologic" response of the fistula and has been shown to be reasonably accurate in predicting success.[3] A study by Herline et al. showed that 52% of patients with fistulas treated with medical therapy achieved a complete response on ultrasound. Of these patients, 64% maintained healing at 1 year thereby predicting success and allowing the result of the treatment to be documented.

Anal disease is often so significant that in-office evaluation is not possible. Therefore, an exam under anesthesia and performance of ultrasound gives a very clear description of the process with minimal psychologic trauma or pain for the patients. In all patients with a perianal abscess, the initial therapy should be drainage and placement of a drain or seton. This is possible in the office under local anesthetic only if the patient can tolerate a moderate amount of pain. A mushroom catheter can be placed and secured for long-term treatment. If incision and

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drainage is performed in the operating room, a soft seton can be placed through the external opening into the internal opening and tied loosely around the intervening skin and muscle. An immediate fistulotomy should only be considered in the case of a superficial posterior fistula.

Drainage of the abscess and long-term observation while on either antibiotics or immune suppressants has been proposed as definitive therapy for perianal Crohn's disease. The most common method of nonoperative treatment is to place a soft noncutting seton through the fistula and to observe the patient. Solomon reported a series of patients in which 79% of the patients treated in this way achieved closure or control (as drainage but no abscess) by 1 year. The patients were evaluated with endorectal ultrasound during placement of the seton. A decrease in anal muscle thickness on the ultrasound was found to be a predictor of success.[4] Unfortunately, the study was inconsistent in its report of adjuvant therapy. A reoperation rate of 11% indicated that this is a reasonable approach to anal fistula disease. St. Mark's Hospital reported long-term follow-up (10 years) of patients treated with simple drainage with seton to result in relapse in 90% of patients.[5] The combination of antibiotics and simple drainage yields an average healing rate of 50% but 50% recur. The most common antibiotics used for treatment of perianal Crohn's fistulas and abscesses are ciprofloxacin and Flagyl. Flagyl may have an immune suppressant effect on the Crohn's disease as well.[1]

Immune suppression and antitumor necrosis factor (TNF) alpha therapy has been shown to result in clinical closure of 46% of fistulas at around 56 weeks of follow-up. However, only 11% of these clinically closed fistulas showed radiologic closure with ultrasound.[6] The combination of infliximab at 5 mg/kg at 0 and 2 weeks with ciprofloxacin and Flagyl seems to be a reasonable approach. The use of ultrasound to show radiologic closure may actually improve outcomes since the ultrasound may be a better indicator of true closure and may predict success.[6] Drainage of the abscess, immune suppression with azathioprine or methotrexate, and infliximab therapy has been shown to yield a 20% sustained fistula closure in Oxford, UK.[7] Proctectomy was required in 25% of these individuals after 21 months of follow-up.

Operative therapy alone Crohn's fistulas has resulted in a 50% long-term healing rate and a 75% short-term healing rate.[1] The most commonly used technique is the mucosal sliding flap repair with coverage of the internal opening after the mucosa has been rendered normal with medical therapy. Van Gemert et al. found that 100% of patients healed when treated with sliding flap repair alone if there is no proctitis present, but 29% of the patients recurred. In a second group of patients with proctitis, if proctitis was resolved using infliximab, 100% patients healed after a sliding flap repair. Only 10% of those patients recurred. This study in a small group of patients indicates that the disease status of the rectum is a very important indicator of success.[8]

Initial experience with the collagen plug as primary treatment for Crohn's fistulas was encouraging. Unfortunately, this experience has not been duplicated in other institutions.[9]

The most recent update of the American Society of Colon and Rectal Surgeons practice parameters for treatment of perianal Crohn's disease from 2005 states: (1) a perianal abscess should be treated in a timely fashion by incision and drainage (level of evidence IVB), (2) asymptomatic Crohn's fistulas need not be treated (level of evidence IVB, (3) simple low Crohn's fistulas may be treated by fistulotomy (level of evidence IVB) and (4) complex Crohn's fistulas may be well-palliated with long-term draining setons (level of evidence IVB), and (5) complex Crohn's fistulas may be treated with advancement flap closure of the rectal mucosa if the rectal mucosa is grossly normal (level of evidence IVB).[10]

The goal of all treatment of Crohn's perianal fistulas should be to preserve the rectum. Therefore, proctectomy for perianal Crohn's disease should be performed in less than 30% of patients. Conservative therapy with setons, sliding flap repairs, and medical therapy using immune suppressants, infliximab, and antibiotics should allow this goal to be achieved.[1,7,11]

Fistulizing disease (arising from the small bowel most commonly) occurs in 30% to 45% of Crohn's patients.[1] These present as abscess, either intra-abdominal, interloop, intramesenteric, or retroperitoneal. The chronic form of this problem is the fistula, either enterocutaneous (15%) or enteroenteric (3%). There are five issues concerning timing of operation for intra-abdominal pyogenic complications of Crohn's disease: When should an operation be performed (1) after perforation, (2) after discovery of an abscess or fistula, (3) after percutaneous drainage has been accomplished, (4) after immune suppressive therapy or anti-TNF alpha therapy has been started, and (5) when considering laparoscopy.

Free perforation occurs very rarely in Crohn's disease. Operation should be emergent on a patient with diffuse peritonitis, abdominal pain, and sepsis. An exploratory laparotomy and construction of an ostomy, with or without bowel resection, is most commonly indicated.

An established abscess should be drained nonoperatively (percutaneously) or through a local transabdominal approach. The abscess should then be allowed to resolve. Percutaneous drainage of a Crohn's related abscess changed our approach to Crohn's disease. A pelvic abscess can safely (2% complication) be drained through a transgluteal approach with no development of fistulas.[12] Abdominal abscesses can be drained transabdominally in 85% to 100% of

cases. If the first effort is unsuccessful, a second try usually is and fistula formation is extremely rare.[13,14] The use of surgical drainage, as opposed to interventional radiology drainage, is also successful. The time to resolution of the abscess has been reported as 22 days, and there is no difference between a surgical or percutaneous approach.[15]

Controversy regarding the need for subsequent operation after abscess drainage continues. At least 30% of patients treated with local drainage will require a definitive operation with resection of the affected segment within 1 year of the drainage procedure due to intractable disease or recurrent abscess.[16] A prolonged time between developing the abscess and the subsequent percutaneous drainage correlates with a higher risk of required operation.[15]

The timing of an operation after drainage of an abscess is influenced by other factors. Malnutrition, the continued presence of an abscess, and the high doses of steroids are independent multivariable factors for increased complications after an operation.[17] In a large meta-analysis of over a thousand patients with strictureplasty, the risk of complication increased only if an abscess was present at the time of the strictureplasty. Any portion of bowel which has a fistula adjacent to the abscess should be resected rather than a strictureplasty performed.[18] Another publication has shown that operating on a perforated terminal ileum within 5 days of the percutaneous drainage if the abscess is completely drained is safe.[14]

Immune suppressants and infliximab can be started very quickly after percutaneous drainage of an abscess. The Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen II trial showed no increase in the incidence of abscess in these patients.[19] A group of 270 patients undergoing operation while receiving infliximab developed few septic complications (19%) or abdominal abscess (2%).[20] Therefore, a time to clear immune suppression before operations is not needed.

Hyperalimentation can be used to successfully convert high risk patients with severe Crohn's disease to elective low risk operations in over 74% of patients. An average of 75 days has been used and shown to be safe with minimal complications.[21]

The use of laparoscopic resection can be safely performed after abscess drainage. However, it should be remembered that there is higher (30%) conversion rate if an abscess is present at the time of laparoscopic procedure.[22] Adhesions due to repeated operation and the presence of ongoing inflammation also result in a higher chance of conversion to open procedure.[23]

In summary, an abscess should be drained and allowed to resolve. Nutrition should be repleted, and inflammation should be reduced as much as possible, even to the extent of using immune suppressants and infliximab in the interim between drainage and operation. A laparoscopic operation is feasible and has been found to be safe after resolution of the abscess and inflammation in an elective setting.[24,25]

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J Gastrointest Surg (2008) 12:2164–2170
DOI 10.1007/s11605-008-0603-y

Timing of Cholecystectomy for Biliary Pancreatitis: Do the Data Support Current Guidelines?

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Received: 29 May 2008 / Accepted: 25 June 2008 / Published online: 18 July 2008

Abstract
Background Current guidelines suggest that cholecystectomy be performed within 2 weeks after discharge following an episode of biliary pancreatitis. We hypothesized that a high incidence of gallstone-related events is present within 2 weeks after discharge prior to cholecystectomy.
Methods Two hundred eighty-one patients who underwent cholecystectomy for biliary pancreatitis (January 1999–December 2005) were categorized into one of two groups: group A patients underwent cholecystectomy during index admission (n=162), and group B patients underwent cholecystectomy following discharge from index admission (n=119).
Results Groups were comparable in demographics, comorbidities, and disease severity. Thirty-nine (32.8%) group B patients experienced pre-cholecystectomy gallstone-related events (including 16 cases of recurrent pancreatitis) after discharge. Recurrences (31.3%) occurred within 2 weeks after discharge. Endoscopic sphincterotomy protected against preoperative recurrent pancreatitis but was associated with a higher incidence of other gallstone-related events. Median total length of hospital stay was greater for group B than for group A [7 (range, 2–37) days vs. 5 (1–45) days, respectively, p=0.00].
Conclusion Current guidelines suggesting the appropriateness of waiting up to 2 weeks for cholecystectomy for biliary pancreatitis may place patients at unacceptably high risk for recurrence. Endoscopic sphincterotomy does not eliminate the risk of gallstone-related events.

Keywords Biliary pancreatitis · Cholecystectomy · Recurrent pancreatitis · Endoscopic sphincterotomy

Portions of this study were presented at the 3rd Annual Academic Surgical Congress, Huntington Beach, CA on February 14, 2008 and at the 42nd Annual Meeting of The Pancreas Club, San Diego, CA on May 18, 2008.

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Abbreviations

ES	endoscopic sphincterotomy
LOS	length of hospital stay
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography

Introduction

In the USA, more than 220,000 patients are admitted to the hospital each year with acute pancreatitis as the primary diagnosis.[1,2] The most common etiology for this condition is gallstones.[1,3,4] Standard recommendations for most patients who have recovered from an episode of gallstone-induced (biliary) pancreatitis include cholecystectomy.[1,3,5–7]

An important consideration in the management of patients with biliary pancreatitis is the timing of cholecystectomy. Current guidelines suggest that cholecystectomy

Table 1 Demographics, Comorbidities, and Severity of Pancreatitis

	Group A (n=162) Cholecystectomy during index admission		Group B (n=119) Cholecystectomy after discharge from index admission		P value
	Number	Percentage	Number	Percentage	
Demographics					
Age (years, median and range)	59 (20–93)		57 (20–99)		0.60
Female	116	71.6	72	60.5	0.05
Patients with comorbidities	33	20.4	25	21.0	0.90
CT severity index					
Mild (no CT, Grade A, B, C)	153	94.4	108	90.8	0.23
Moderate to severe (grade D, E)	9	5.6	11	9.2	0.23
Severe acute pancreatitis	0	0	2	1.7	0.10

CT computed tomography

be performed within 2 weeks after resolution of an episode of biliary pancreatitis. For example, guidelines put forth by the UK Working Party on Acute Pancreatitis[7] recommend that cholecystectomy should not be delayed more than 2 weeks after discharge from index admission for acute pancreatitis. The American Gastroenterological Association guidelines[5] suggest that cholecystectomy should be performed within 2–4 weeks after discharge from index admission. Other guidelines, such as those published by the American College of Gastroenterology[6], fail to make recommendations on timing of cholecystectomy after resolution of acute biliary pancreatitis.

We believe that these guidelines may not be stringent enough with respect to timing of cholecystectomy. In this study, we tested the hypothesis that there is a high incidence of gallstone-related events, including recurrent pancreatitis, within 2 weeks after discharge following an episode of biliary pancreatitis in the absence of cholecystectomy.

Material and Methods

This study was conducted with the approval of the Brigham & Women's Hospital Institutional Review Board.

Medical records of all 891 patients admitted with the diagnosis of acute pancreatitis at our institution from January 1995 through December 2005 were analyzed [patients were identified using the ICD-9 code for acute pancreatitis (577.0)]. The diagnosis of acute pancreatitis was based on the presence of symptoms and signs of pancreatitis (e.g., abdominal pain and tenderness) together with elevations in serum amylase and/or lipase concentration (to at least three times the upper limit of normal).[7]

Three hundred fifty-five of these patients were classified as having had acute pancreatitis of biliary etiology based on the documentation of gallstones or choledocholithiasis on imaging studies[1–3] and underwent cholecystectomy following their biliary pancreatitis episode. Thirty-five of these patients, whose biliary pancreatitis was initially managed at an outside hospital, were excluded from further analysis. Further, we excluded patients documented to have necrotizing pancreatitis on contrast-enhanced computed tomography (CT) scan (n=39), as the management of patients with necrotizing pancreatitis is distinct and has been the subject of previous reports.[3,7,8]

Thus, 281 patients comprise our study sample. These patients were categorized into one of two groups: group A patients underwent cholecystectomy during index admission (during which pancreatitis was diagnosed, n=162), and

Table 2 Gallstone-Related Events after Discharge, Prior to Cholecystectomy, in Group B

Group B (n=119) Cholecystectomy after discharge from index admission	Number	Percentage
All gallstone-related events	39	32.8
Recurrent pancreatitis	16	13.4
Biliary colic	14	11.8
Acute cholecystitis	6	5.0
Jaundice	2	1.7
Cholangitis	1	0.8

Table 3 Interval Between Discharge to Gallstone-Related Events

	All gallstone-related events (n=39)		Recurrent pancreatitis (n=16)	
	Number	Percentage	Number	Percentage
Within 1 week	2	5.1	2	12.5
Within 2 weeks	7	17.9	5	31.3
Within 3 weeks	10	25.6	7	43.8
Within 4 weeks	14	35.9	8	50.0

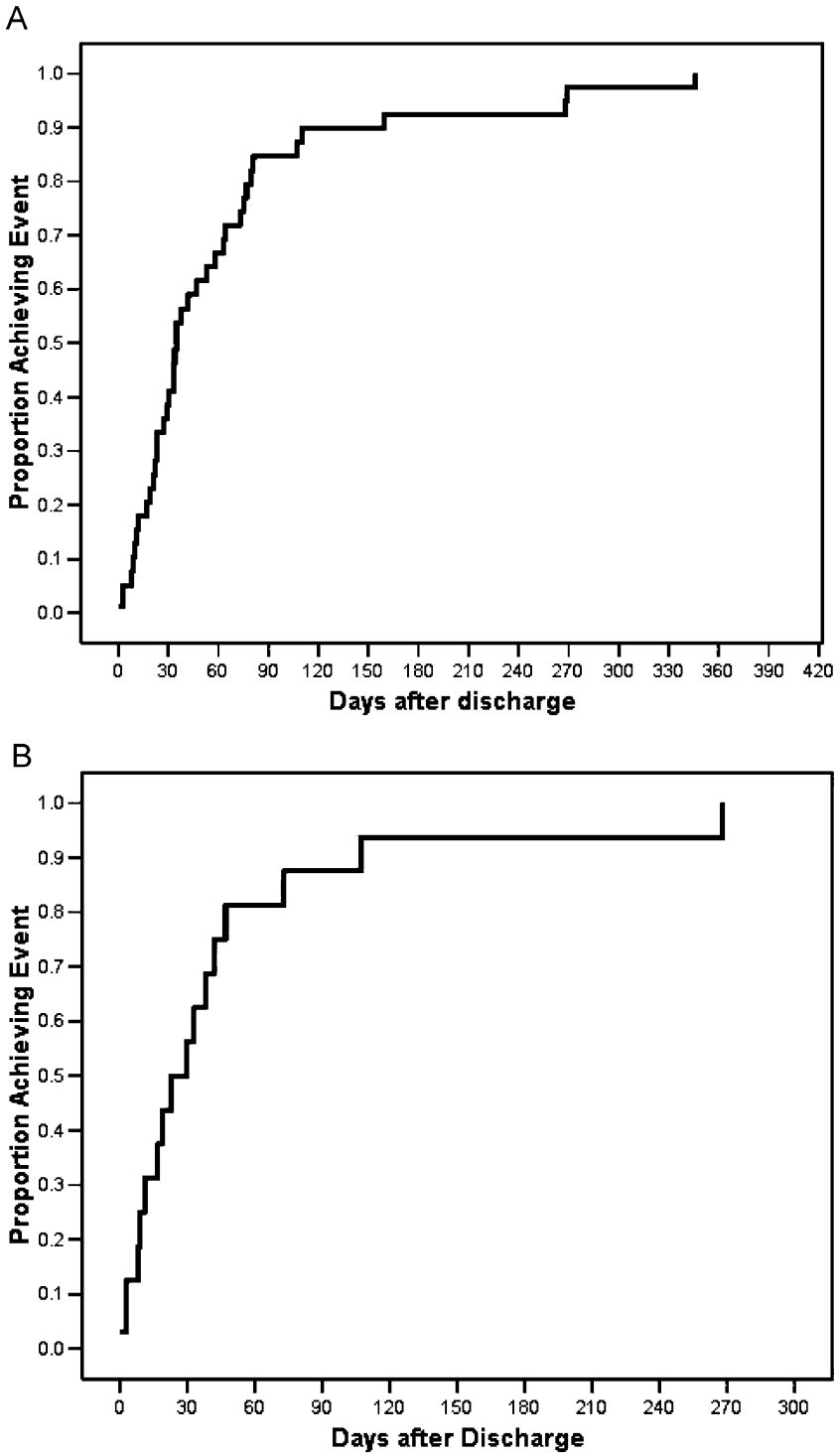

Figure 1 Kaplan–Meier representations of interval (days) between discharge to all gallstone-related events (**A**) and interval (days) between discharge to pancreatitis recurrence (**B**).

group B patients underwent cholecystectomy following discharge from index admission (n=119).

Incidence and timing of gallstone-related events, including recurrent acute pancreatitis, total length of hospital stay (LOS; index admission + admissions for recurrences and for cholecystectomy), and perioperative morbidity and mortality rates were analyzed. Data were evaluated using two-tailed Student's t test, chi-square test, and Fisher's exact test as appropriate. Criteria for statistical significant was $p<0.05$.

Table 4 ES and Gallstone-Related Events

	ES performed (n=42)		ES not performed (n=77)		P value
	Number	Percentage	Number	Percentage	
Demographics					
Age (years, median and range)	52 (19–89)		55 (20–92)		0.711
Female	30	71.4	42	54.5	0.072
Patients with comorbidities	22	52.4	50	64.9	0.181
CT severity index					
CT not performed	23	54.8	33	42.9	0.214
A	0	0.0	0	0.0	–
B	11	26.2	19	24.7	0.856
C	7	16.7	15	19.5	0.706
D	1	2.4	9	11.7	0.080
Gallstone-related events					
Total incidence	14	33.3	25	32.5	>0.99
Recurrent pancreatitis	2	4.8	14	18.2	0.049
Acute cholecystitis	5	11.9	1	1.3	0.020
Jaundice	2	4.8	0	0	0.123
Cholangitis	1	2.4	0	0	0.353
Biliary colic	4	9.5	10	13.0	0.768

ES endoscopic sphincterotomy, *CT* computed tomography

Results

Groups were comparable in demographic variables, comorbidity rates, and disease severity as indicated by CT severity index[9] and the percentage of patients with severe acute pancreatitis as defined by the Atlanta Symposium (Table 1).[10] Median interval from diagnosis of acute pancreatitis to cholecystectomy was greater among group B than among group A patients [45 days (range, 4–346 days) vs. 3 days (range, 0–43 days), respectively, $p<0.001$].

Thirty-nine (32.8%) group B patients experienced gallstone-related events, including 16 cases of recurrent pancreatitis, following discharge from index admission but prior to cholecystectomy (Table 2). Median interval from discharge to any gallstone-related events was 33 days (range, 1–346 days). Median interval from discharge to recurrent pancreatitis was 19 days (range, 1–268 days). Recurrences (12.5%) occurred within 1 week, 31.3% occurred within 2 weeks, and 50% occurred within 4 weeks after discharge (Table 3). These findings are shown graphically in the Kaplan–Meier curves in Fig. 1A and B.

Preoperative endoscopic retrograde cholangiopancreatography (ERCP) was performed in 64 (39.5%) group A patients and in 56 (47.1%) group B patients (p=0.21). ERCP with endoscopic sphincterotomy (ES) is widely believed to protect against recurrent pancreatitis in patients with biliary pancreatitis.[2,5–7] To assess the efficacy of this procedure in preventing gallstone-related events in patients not undergoing cholecystectomy during index admission, we compared the 42 (35.3%) group B patients who underwent ES during index admission to those who did not undergo this procedure. As shown in Table 4, ES

Table 5 Operative Procedures

	Group A (n=162) Cholecystectomy during index admission		Group B (n=119) Cholecystectomy after discharge from index admission		P value
	Number	Percentage	Number	Percentage	
Laparoscopic cholecystectomy	124	76.5	95	79.8	0.51
Laparoscopic to open conversion	20	12.3	8	6.7	0.12
Open cholecystectomy	16	9.9	14	11.8	0.61
Open cholecystectomy + CBD exploration	2	1.2	2	1.7	0.76

CBD common bile duct

protected against, but did not eliminate, preoperative recurrent pancreatitis. Further, it was associated with a significantly higher incidence of acute cholecystitis.

Table 5 shows operative procedures performed. Groups A and B did not differ with respect to the percentages of patients undergoing these various procedures.

Perioperative outcomes are shown in Table 6. Median total LOS (including index admission plus admissions for pre-cholecystectomy recurrences plus admission for cholecystectomy) was greater for group B than for group A patients. In group B, median LOS for index admission for acute pancreatitis was 4 days (range, 1–34 days), median LOS for readmissions due to pre-cholecystectomy gallstone-related events was 3 days (range, 1–19 days), and median LOS for cholecystectomy was 1 day (range, 1–28 days). Postoperative reoperation was more frequent for group B than for group A patients. There were no mortalities in either group.

There were four patients (all of whom were in group B) who needed reoperations. Two of them underwent pancreatic debridement for recurrent pancreatitis (with necrosis). One patient was explored for postoperative hemorrhage, and one patient was explored for a bile leak.

Discussion

High-quality evidence[11–16] suggests that cholecystectomy should be offered to most patients diagnosed with biliary pancreatitis. However, data relevant to determining the optimal timing of cholecystectomy in these patients are limited.[17–24] As a result, available guidelines vary with respect to recommendations on timing of cholecystectomy.[5–7,25–29] Indeed, there is no consensus on whether or not patients who suffer an episode of acute gallstone pancreatitis can be safely discharged prior to undergoing cholecystectomy.

Our study demonstrates that delaying cholecystectomy until after discharge from index admission can be associated with a high incidence of gallstone-related events (including recurrent pancreatitis), prolonged overall LOS, and adverse postoperative outcomes. Importantly, more than 30% of pancreatitis recurrences in our cohort occurred within 2 weeks after discharge from index admission.

Preoperative gallstone-related events were clinically significant in that they prompted emergency department visits in each of the patients in which they occurred. All 16 patients with pre-cholecystectomy recurrent pancreatitis had symptoms severe enough to warrant in-hospital evaluation. Patients who underwent delayed cholecystectomy had longer overall LOS than patients who underwent cholecystectomy during index admission because 33% of them required at least one separate pre-cholecystectomy readmission for gallstone-related events. These readmissions could have been prevented had cholecystectomy been performed at initial admission.

Previous reports relevant to our findings are limited to small series. Taylor and Wong[22] reported postoperative outcomes for 46 patients who underwent cholecystectomy following an episode of biliary pancreatitis. Patients treated by a surgeon who preferred early surgery had shorter average hospital stay than patients treated by a surgeon who preferred delayed surgery; however, no differences in morbidity rates between these two groups were evident. In another study reported by Alimoglu et al.,[23] 27 patients who underwent cholecystectomy during index admission for biliary pancreatitis had a shorter mean LOS and a lower morbidity rate than 16 patients who underwent cholecystectomy only after suffering a post-discharge recurrence of pancreatitis. Findings of these studies[22,23] have been interpreted to support early cholecystectomy; however, these reports failed to provide information on timing of recurrence as a function of time following discharge from hospital. As a result, inferences on optimal timing of cholecystectomy were extrapolations at best.

Our study also demonstrated that ES does not eliminate the risk of pancreatitis recurrence or other gallstone-related events. These findings are discordant with recommendations suggesting that ES can serve as an alternative to, and

Table 6 Perioperative Outcomes

	Group A (n=162) Cholecystectomy during index admission		Group B (n=119) Cholecystectomy after discharge from index admission		P value
	Number	Percentage	Number	Percentage	
Length of hospital stay (days, median and range)	5 (1–45)		7 (2–37)		<0.001
Readmission after operation	16	9.9	12	10.1	0.95
Reoperation	0	0	4	3.4	0.02
Morbidity	37	22.8	34	28.6	0.27
Mortality	0	0	0	0	–

thus can eliminate the need for, cholecystectomy in patients with biliary pancreatitis.[30–32] However, our findings are consistent with those of a randomized clinical trial reported by Boerma et al.[11] in which patients who underwent ES alone for biliary pancreatitis were compared against those who underwent ES and cholecystectomy. Forty-seven percent of patients who underwent ES alone suffered recurrent biliary symptoms during 2-year follow-up, whereas only 2% of patients who had cholecystectomy did so. Of course, ES alone does continue to have a role for patients with biliary pancreatitis who are unfit for surgery. Such patients can be expected to have a 1% probability of developing recurrent pancreatitis and an 8–17% probability of developing other biliary events.[30,31,33–38]

Limitations of our analysis include the retrospective study design and sample size considerations. However, ours is among the largest series to assess the timing of cholecystectomy for biliary pancreatitis yet reported. Further, our study groups were comparable with respect to demographic variables, comorbidity rates, and disease severity. To date, no prospective randomized trials evaluating timing of cholecystectomy have been reported. Until data from such studies are available, we must base clinical decision making on available evidence.

It is important to remember that our findings are relevant only to mild acute pancreatitis, as we excluded most patients with severe disease from our analysis. There is ample evidence, including data from at least one prospective clinical trial, to recommend delayed cholecystectomy among patient with severe acute pancreatitis of biliary etiology.[6,7,17–19,25,34,39–42]

Conclusion

Current guidelines suggesting the appropriateness of waiting up to 2 weeks for cholecystectomy following discharge from index admission for biliary pancreatitis may place patients at unacceptably high risk for recurrence. ES does not eliminate the need for cholecystectomy in these patients.

Acknowledgment The authors thank to Jan Rounds for her excellent secretarial assistance.

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J Gastrointest Surg (2008) 12:2171–2176
DOI 10.1007/s11605-008-0584-x

MicroRNA-21 is Overexpressed in Pancreatic Cancer and a Potential Predictor of Survival

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Received: 25 April 2008 / Accepted: 16 June 2008 / Published online: 19 July 2008

Abstract
Background MicroRNAs are small (18–22 nucleotides) noncoding RNAs involved in posttranscriptional modification of many target genes. One of these, microRNA-21 (miR-21), has been shown to play a role in multiple hematologic and solid organ malignancies. We sought to determine the expression pattern of miR-21 in pancreatic cancers and its impact on clinicopathologic characteristics.
Methods Eighty resected pancreatic cancer specimens were microdissected and tissue microarrays (TMA) created in duplicate. TMAs were also created for benign pancreas (N=12) and chronic pancreatitis (N=45). In situ hybridization (ISH) was undertaken utilizing locked nucleic acid probes for miR-21. RNA U6 and scrambled RNA served as positive and negative control, respectively. ISH was scored as 0 (absent), 1+ (faint/focal expression), or 2+ (strong expression). Kaplan–Meier survival curves were constructed and compared by log-rank analysis.
Results MiR-21 expression was demonstrated in 63 (79%) pancreatic cancers (1+ in 49, 2+ in 14) compared to one of 12 (8%, p<0.0001) benign pancreas and 12/45 (27%, p<0.0001) chronic pancreatitis. None of the benign tissues demonstrated strong miR-21 expression. Although miR-21 expression did not correlate with tumor size, differentiation, nodal status, or T stage, strong miR-21 expression was predictive of poorer outcome compared to absent or faint/focal miR-21 expression in patients with node-negative disease (median 27.7 months vs. 15.2, p=0.037). Nodal status was also predictive of survival (p=0.029).
Conclusions MicroRNA-21 is significantly overexpressed in pancreatic cancers as detected by in situ hybridization. Its strong expression predicts limited survival in patients with node-negative disease and may be an important biologic marker for outcome.

Keywords MicroRNA · MiRNA · MiR-21 · Pancreatic cancer

Presented at American Hepato-Pancreato-Biliary Association Annual Meeting in Ft. Lauderdale, FL, March 27, 2008.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States. It is nearly uniformly fatal with its yearly mortality approaching its incidence with over 33,000 people succumbing from the disease in 2007.[1] Chemoradiation has been shown to modestly prolong survival; however, the prognosis remains extremely poor with the median survival less than 24 months.[2] These factors have led to the research and need to discover unique molecular targets and biologic therapies for pancreatic cancer.

MicroRNAs (miRNAs or miRs) are small (~18–22 nucleotides) noncoding RNAs which have critical functions in various biological processes.[3] Over 450 human miRNAs have been reported and a number of them have been shown to play normal physiologic roles in cell proliferation,

apoptosis, and differentiation. These naturally occurring miRNAs function by binding to target mRNAs, resulting in their degradation or translational inhibition based upon the degree of complimentarity with their target mRNA.[4] MiRNAs have been proposed to contribute to oncogenesis by promoting the expression of oncogenes or by inhibiting tumor suppressors.[5] These dysregulated miRNAs are often referred to as *oncomiRs*.

One such oncomiR, miR-21 has been shown to be overexpressed in multiple malignancies including pancreatic cancer,[6,7] esophageal cancer,[8] lung cancer,[9] and colon cancer.[10] This miRNA has been linked to tumor aggression and carcinogenesis, in part, by preventing apoptosis and, thus, functioning as an oncogene.[11,12] Previous studies have primarily used real time polymerase chain reaction (RT-PCR) or miRNA microarray technology to evaluate miRNA expression.[13,14] The small size of mature miRNA leads to a low melting temperature of the miR/cDNA complex that is difficult to detect using in situ hybridization.[15] Thus, in situ hybridization had not been used extensively to evaluate miRNA expression previously. This problem has been addressed by modifying the nucleotide bases with locked nucleic acids which markedly increases the melting temperature of the miR/cDNA probe.[14] While very sensitive for miRNA detection, RT-PCR and microarray chip technologies are unable to differentiate between expressions from malignant cells vs. contamination from surrounding stroma. This is especially important to distinguish in pancreatic cancer where the surrounding stroma demonstrates such an intense inflammatory reaction.

Herein, we sought to utilize in situ hybridization to answer two important questions. First, in pancreatic cancers, is tumor miR-21 expression derived primarily from malignant ductal epithelial cells or surrounding stroma? Secondly, does miR-21 expression predict survival in patients undergoing curative resection for pancreatic cancer?

Materials and Methods

Tissue Microarrays

After approval from the institutional review board, 80 formalin-fixed, paraffin-embedded pancreatic cancer specimens, 12 benign pancreas, and 45 chronic pancreatitis samples were obtained from the Department of Pathology's archival files at Ohio State University. Samples were microdissected and tissue microarrays (TMAs) were created in duplicate. Our method of TMA creation has been described previously.[16] Briefly, 2 mm cores were punched out of each paraffin block in duplicate and transferred to the recipient TMA blocks using a precision instrument (Beecher Instruments, Silver Springs, MD, USA). The paraffin-embedded tissues were then cut in 4 μm slices and placed on a positively charged slide. The slides were heated to 40°C for 30 min, then leveled off and cooled to 4°C for 15 min.

In Situ Hybridization

The in situ hybridization was carried out with probes for miR-21 as well as appropriate controls. The TMA slides were incubated at 60°C for 30 min, deparaffinized in xylene, and rehydrated with graded alcohol washes. Subsequently, the slides were fixed in 4% paraformaldehyde at 4°C for 10 min and then washed three times in phosphate buffered saline (PBS). The slides were then incubated in Proteinase K solution at 37°C for 20 min. After rinsing, they were immersed in formaldehyde for 10 min. The slides were prehybridized in hybridization buffer (no probe) at 53°C for 1 h. Digoxigenin (DIG)-labeled mercury locked nucleic acid probes for miR-21, U6 (positive control), and scrambled RNA (negative control; Exiqon, Woburn, MA) were hybridized to the slides for 20 h at 53°C. Strigency washes were performed at 53°C and the slides were then placed in a blocking solution for 1 h at room temperature. Sections were then incubated for 2 h at room temperature with preincubated blocking solution with alkaline phosphatase conjugated anti-DIG Fab fragment. After washing in 0.1% Tween-20 followed by PBS, they were stored at 4°C until the following day. The slides were then blotted and layed flat in a humidified chamber and subsequently incubated for 10 h with RTU BM purple AP substrate (Roche, Basel, Switzerland) at room temperature. The slides were then placed in stop solution for 5 min and mounted. Only the slides that stained appropriately for the controls were analyzed. The slides were then scored by two pathologists independently as negative (−), weak or focally positive (1+), or strongly positive (2+). Both pathologists were blinded to the patient's clinical outcome.

Data Acquisition and Statistics

Patient demographics, clinical presentation, hospital course, and outcome were extracted from hospital records. Data collected included age, gender, presence of jaundice, tumor size, T stage, nodal status, differentiation, and postoperative complications. Survival data was obtained from hospital and clinic records and the Social Security Death Index (http://www.ssdi.rootsweb.ancestry.com) as of February 14, 2007. Kaplan–Meier survival curves were constructed and compared by log-rank analysis. Categorical data were compared by Fisher's exact test.

Table 1 MiR-21 Expression by In Situ Hybridization

miR-21 expression	PCA (N=80)	CP (N=45)	NP (N=12)
0 (negative)	17 (21%)	33 (73%)	11 (92%)
1+ (weak positive)	49 (61%)	12 (27%)	1 (8%)
2+ (strong positive)	14 (18%)	0 (0%)	0 (0%)
All positive	63/80 (79%)	12/45 (27%)*	1/12 (8%)*

*p<0.0001 vs. pancreatic cancer

Results

MiR-21 expression was demonstrated in 63 (79%) of the pancreatic cancers by in situ hybridization (Table 1). While most of the cancers demonstrated 1+ miR-21 expression, 14 had 2+ expression. MiR-21 expression was significantly less common in normal pancreas (8%, p<0.0001) and chronic pancreatitis (27%, p<0.0001; Fig. 1). In all cancer specimens, miR-21 expression was seen only in tumor cells and not in the surrounding stroma. None of the benign tissues (i.e., normal pancreas or chronic pancreatitis) demonstrated strong miR-21 expression. MiR-21 staining was seen predominately in the nuclei with some cytoplasmic stipling (Figs. 2 and 3).

MiR-21 expression did not correlate with tumor size, differentiation, nodal status, or T stage. Of all variables tested, only T stage and nodal status were predictive of survival. A median survival of 14.3 months was seen in patients with positive nodes compared to 23.1 months for patients with node-negative disease (p=0.029; Fig. 4; Table 2). When miR-21 expression was considered in all pancreatic cancer patients, it was not a significant predictor of survival. However, in the subset of patients with node-negative disease, strong miR-21 expression was predictive of poorer outcome compared to absent or faint/focal miR-21 expression (Fig. 5). Those with node-negative disease and strong miR-21 expression had a median survival of 15.2 vs. 27.7 months for those who did not strongly overexpress miR-21 (p=0.037; Table 3).

Discussion

MiRNA profiles have been established for many solid and hematologic malignancies. In particular, miR-21 has been reported to be important in many cancers but associations

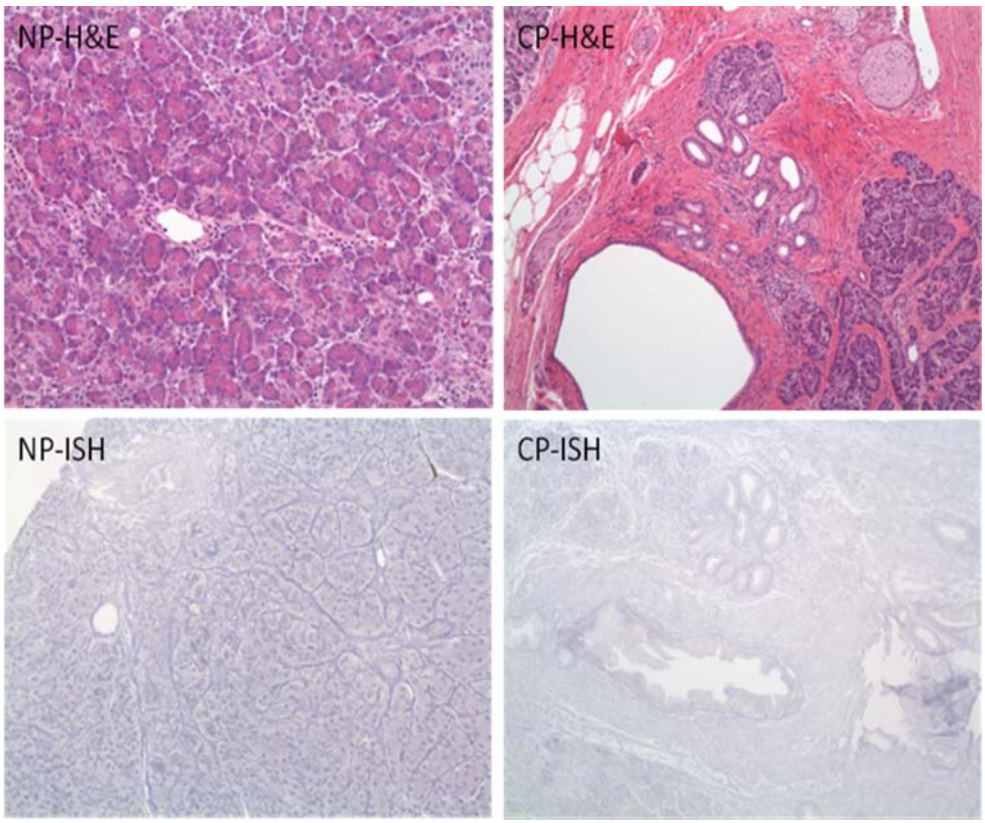

Figure 1 Hematoxylin and eosin stain (*top panels*) and in situ hybridization (*bottom panels*) for miR-21 in normal pancreas (*NP*) and chronic pancreatitis (*CP*) at ×40 magnification. No staining is seen for miR-21.

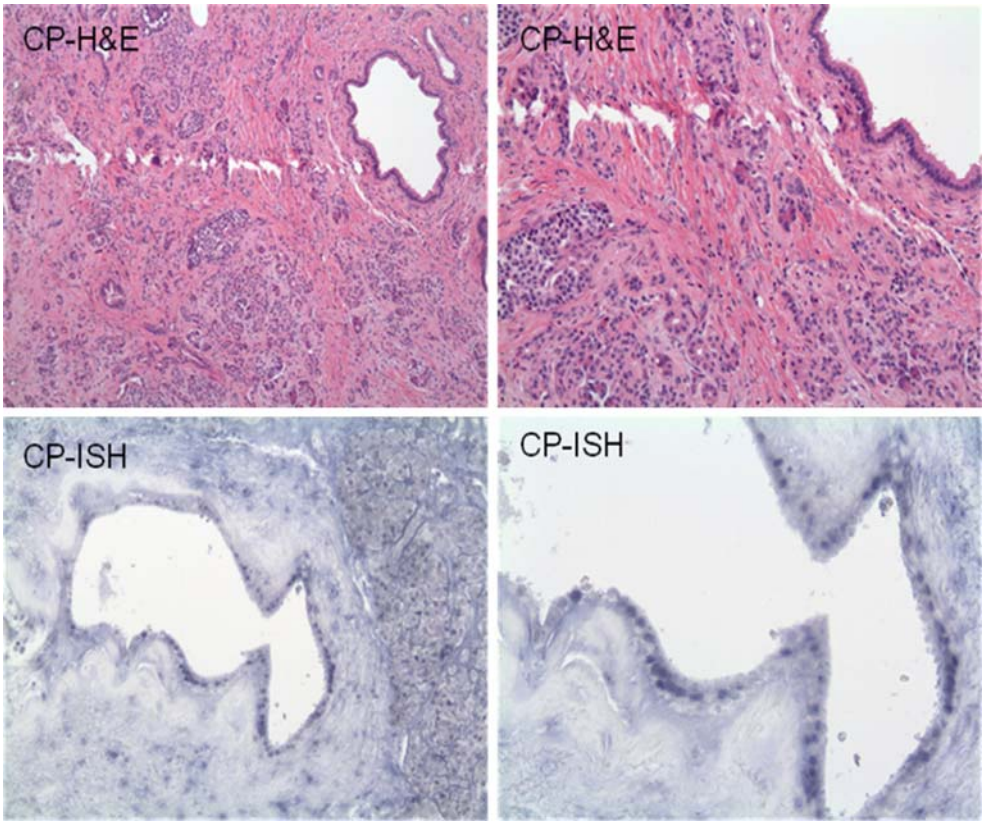

Figure 2 Hematoxylin and eosin stain (*top panels*; ×40 magnification) and in situ hybridization (*bottom panels*; ×100 magnification) in chronic pancreatitis with 1+ expression of miR-21. Note darker nuclear staining in ductal epithelial cells.

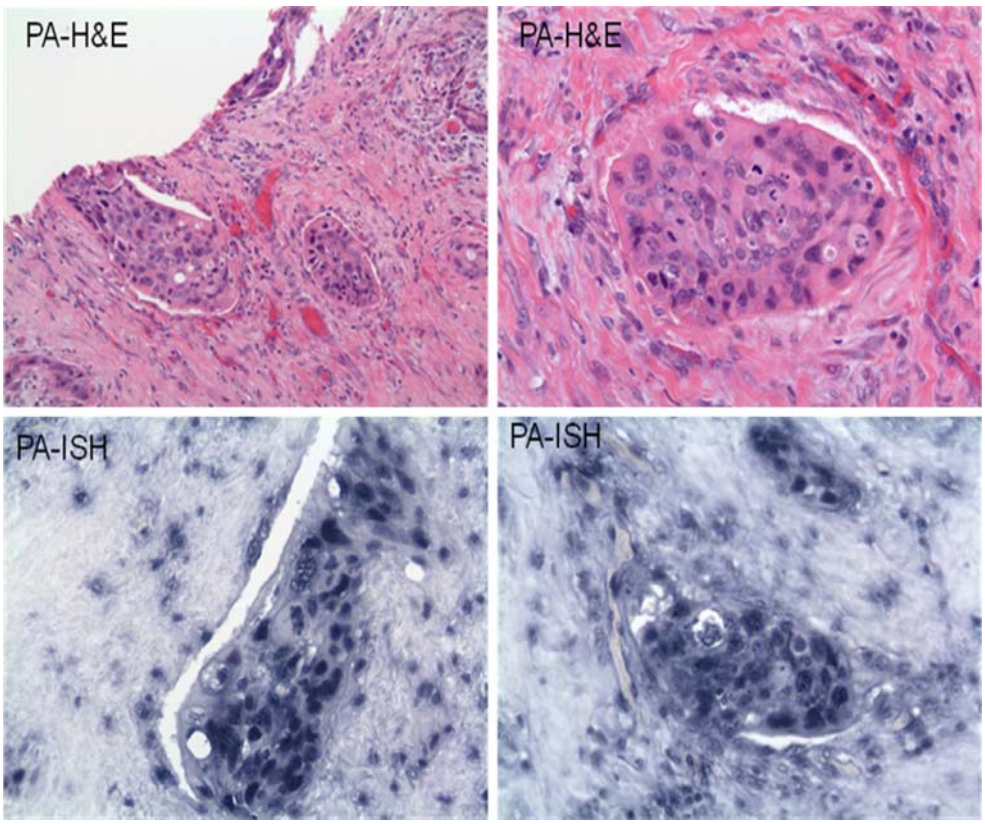

Figure 3 Hematoxylin and eosin stain (*top panels*; ×40 magnification) and in situ hybridization (*bottom panels*; ×100 magnification) of pancreatic adenocarcinoma (*PA*) with 2+ miR-21 expression. Note dark nuclear staining with cytoplasmic stipling, predominately in cancer cells with very little stromal staining.

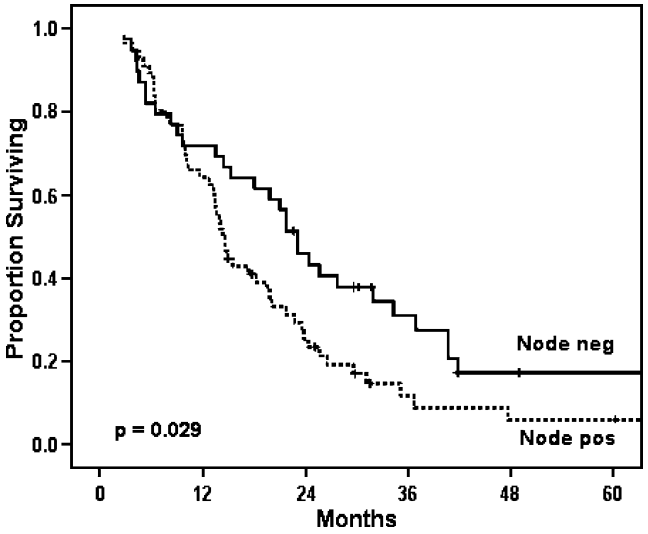

Figure 4 Overall survival curves for node-positive and node-negative pancreatic cancers.

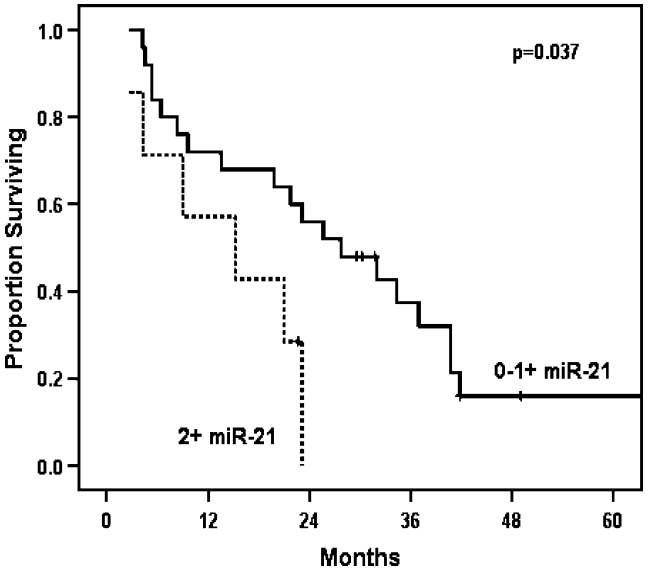

Figure 5 Overall survival in node-negative patients strong vs. weak or no expression of miR-21.

with clinical outcomes and survival are largely unknown. Similarly, few biological markers have been shown to predict survival in pancreatic cancer, likely due to a universally poor prognosis. In this study, we show that strong miR-21 expression in pancreatic cancer by in situ hybridization may be predictive of poor survival in a group of patients that would otherwise be considered as having a favorable pathology (i.e., nodes negative).

We have previously shown that miR-21 is significantly overexpressed in pancreatic cancer using miRNA microarray technology.[5] While microdissection was utilized to minimize contamination by surrounding stroma, the intense inflammatory reaction often associated with pancreatic cancer calls into question the cell of origin for miR-21 expression. In the present study using in situ hybridization, tumoral miR-21 expression was only seen in malignant cells and not in the surrounding stroma. Interestingly, when miR-21 was expressed, albeit weakly, in benign pancreas, it was only seen in ductal epithelial cells. Staining was predominately nuclear, suggesting binding to precursor miR-21 as well as the mature sequence seen in the cytoplasm. Given that a strong correlation between precursor and mature miRNA has been shown previously, such nuclear staining is not surprising.[17]

Not clear in this study still is whether miR-21 expression plays a role in oncogenesis in pancreatic cancer or is a late event, perhaps even being incited by reactive stromal cells. The low expression levels seen in the chronic pancreatitis specimens suggest that miR-21 expression is fairly specific to malignancy, however. Our previous microarray data demonstrated that miR-21 expression is able to discriminate, in part, between chronic pancreatitis and pancreatic cancer.[6] Hence, miR-21 appears to play an important role in carcinogenesis.

MiR-21 expression did not correlate with tumor size, differentiation, nodal status, or T stage. As expected, the presence of metastatic disease in the lymph nodes decreased survival significantly. When all patients were considered, miR-21 expression did not have an impact on survival. However, in the patients who were expected to have the best survival (i.e., those with lymph node-negative disease), strong overexpressed of miR-21 was associated with a significantly decreased median, 1-, and 5-year overall survival. The subset of patients in this study with node-negative disease is quite small and, therefore, a larger study to confirm these data is necessary and underway. These findings could be helpful in determining which patients should receive the most aggressive treatments and serve as an important biological marker of outcome.

Table 2 Overall Survival Based Upon Nodal Status

	Median (months)	1 year (%)	5 year (%)
Node negative	23.1	71.8	17.2
Node positive	14.3	64.3	5.8

Table 3 Overall Survival in Node-Negative Patients with Strong vs. Weak or No Expression of miR-21

miR-21	Median (months)	1 year (%)	5 year (%)
0–1+	27.7	72	16
2+	15.2	57.1	0

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J Gastrointest Surg (2008) 12:2177–2182
DOI 10.1007/s11605-008-0605-9

Distal Pancreatectomy is Not Associated with Increased Perioperative Morbidity when Performed as Part of a Multivisceral Resection

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Received: 8 March 2008 / Accepted: 8 July 2008 / Published online: 2 August 2008

Abstract
Purpose To evaluate the indications for and the outcomes from distal pancreatectomy.
Methods Retrospective chart review of 171 patients who underwent distal pancreatectomy at Brigham and Women's Hospital between January 1996 and August 2005.
Results Nearly one-third of distal pancreatectomies were performed as part of an en bloc resection for a contiguous or metastatic tumor. Fifty-six percent of the patients underwent a standard distal pancreatectomy +/− splenectomy (group 1), whereas 44% of distal pancreatic resections included additional organs or contiguous intraperitoneal or retroperitoneal tumor (group 2). The overall post-operative complication rate was 37%; the most common complication was pancreatic duct leak (23%). When compared to patients undergoing standard distal pancreatectomy, those with a more extensive resection including multiple viscera and/or metastatic or contiguous tumor resection had no significant difference in overall complication rate (35% v. 39%, $p=0.75$), leak rate (25% v. 20%, $p=0.47$), new-onset insulin-dependent diabetes mellitus (3% v. 4%, $p=1.0$), and mortality (2% v. 4%, $p=0.656$).
Conclusion This series includes a large number of patients in whom distal pancreatectomy was performed as part of a multivisceral resection or with en bloc resection of contiguous tumor. Complications were no different in these patients when compared to patients undergoing straightforward distal pancreatectomy.

Keywords Distal pancreatectomy · Multivisceral resection · Pancreatic fistula

Introduction

Distal pancreatectomy is performed for a variety of indications ranging from trauma to malignant neoplasms. Several studies have demonstrated very low mortality rates after distal pancreatectomy, with some high-volume centers showing mortality rates of 0% to 4%.[1–3] Nevertheless, morbidity remains high, ranging from 10% to 47%.[4] Pancreatic leak or fistula is one of the most common complications following distal pancreatectomy.[1,3,5] Although several different definitions of pancreatic leak have been utilized amongst different studies, complicating comparisons across different series, pancreatic leak or fistula rates have been reported to range from 0% to 64% after this procedure.[4] In 2005, an international study group adopted a universal definition of pancreatic leak that should facilitate comparison across different studies.[6]

In addition to resection of isolated tumors of the pancreatic tail, distal pancreatectomy is performed for locally advanced primary and metastatic non-pancreatic neoplasms for potential cure as well as palliation.[7] Data

Poster presentation: DDW/SSAT Poster Session: Clinical/Pancreas—May 22, 2006 Los Angeles, CA.

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suggest that distal pancreatectomy with en bloc resection of contiguous structures can be achieved with acceptable morbidity and mortality,[7] as can distal pancreatectomy for rare metastatic tumors to the pancreas.[8] Still, it is unclear whether these potentially more complex procedures share the favorable outcomes that have been demonstrated with straightforward distal pancreatectomy.

Given a broad experience with this procedure at our institution, we sought to evaluate our indications for and outcomes of distal pancreatectomy in the last decade. Our experience with distal pancreatectomy is somewhat unique due to the relatively high number of procedures performed for non-pancreatic tumors and a large number of pancreatectomies performed as part of a multivisceral resection for contiguous tumor. Given this experience, we wished to compare our experience with standard distal pancreatectomy to distal pancreatectomy associated with contiguous organ resection or metastatic non-pancreatic tumors.

Materials and Methods

Patients

We conducted a retrospective review of all patients who underwent distal pancreatectomy from January 1996 to August 2005 using the ICD-9 code (52.52) for distal pancreatectomy. Our database consisted of 171 consecutive patients who underwent distal pancreatectomy at Brigham and Women's Hospital. Approval was obtained from Brigham and Women's Hospital Institutional Review Board/Partners Human Research Committee. Demographic, clinical, operative, and pathologic details were collected. Pre-operative indications and post-operative complications were recorded.

Statistical Analysis

Pancreatic leak was broadly defined according to the post-operative pancreatic fistula international study group definition as any measurable volume of drain fluid on or after post-operative day 3 with an amylase content greater than three times the upper normal serum value.[6]

Statistical analysis was performed using Fisher's exact test where appropriate. A p value <0.05 was considered statistically significant.

Patients who underwent straightforward distal pancreatectomy with or without splenectomy (group 1) were compared to patients with more extensive or multivisceral resections (group 2). The second group included patients who underwent distal pancreatectomy due to contiguous involvement of the pancreas from other primary tumors as well as patients who underwent distal pancreatectomy for resection of metastases to the pancreas.

Results

Patient Demographics

From January 1996 to August 2005, over the 10-year period of our evaluation, 171 patients underwent distal pancreatectomy. The mean age of the patients at time of operation was 54±14 years (median age 55 years; range 17–83 years) old (Table 1).

Indications

The indications for distal pancreatectomy included contiguous or metastatic tumor in 52 patients (30%), cystic neoplasm in 39 patients (23%), pancreatic mass in 36 patients (21%), chronic pancreatitis in 13 patients (7.6%), neuroendocrine tumor in 11 patients (6.4%), and miscellaneous reasons (e.g., trauma, pseudocyst, pancreatic necrosis, etc.) in 20 patients (12%). Indications for distal pancreatectomy are presented in Table 2.

Operative Details

The median post-operative length of stay was 7 days. Mean post-operative length of stay was 11 days. Median post-operative length of stay was 6 days for group 1 and 9 days for group 2. Mean post-operative length of stay was 9 days for group 1 and 13 days for group 2.

Distal pancreatectomy +/− splenectomy was performed in 96 patients (56%), whereas 75 patients (44%) underwent larger resections that included distal pancreatectomy plus resection of additional organs or contiguous intraperitoneal or retroperitoneal tumors. More extensive resections were performed for both pancreatic and non-pancreatic primaries. These procedures included a diverse combination of multivisceral resections. The most common extensive resections included partial or total gastrectomy in 29 patients (39%), partial colectomy in 25 patients (33%), nephrectomy in 17 patients (23%), resection of retroperitoneal tumor in 16 patients (21%), and small bowel resection in 14 patients (19%). Table 3 details the extent of multivisceral resections.

Table 1 Demographics

Demographics	Values
Age	
Mean	54±14 years
Median	55 years
Range	17–83 years
Gender	
Female	97 (57%)
Male	74 (43%)

Table 2 Pre-operative Indications for Distal Pancreatectomy in 171 Patients

Indication	Number	%
Cystic neoplasm	39	23
Pancreatic mass	36	21
Chronic pancreatitis	13	7.6
Neuroendocrine tumor	11	6.4
Contiguous/metastatic tumor	52	30
Other	20	12

Although 12 procedures were attempted laparoscopically, only six patients underwent a laparoscopic distal pancreas resection (two strictly laparoscopic and four hand-assisted/lap-assisted). The pancreatic stump was stapled in 76 patients (45%), oversewn in 38 patients (22%), and both stapled and oversewn in 55 patients (33%). All patients except for two had either a Jackson–Pratt or a Blake drain placed.

Final Pathology

The final pathology of the resected specimens is found in Table 4. Most commonly, in 49 patients (29%), the pathology revealed a non-pancreatic tumor such as contiguous spread from adjacent structures or metastasis from other sites. Table 3 summarizes the pathologic findings. Other common pathologic findings included mucinous cystadenoma in 20 patients (12%), chronic pancreatitis in 19 patients (11%), pancreatic adenocarcinoma in 19 patients (11%), neuroendocrine tumors in 17 patients (9.9%), and serous cystadenoma in eight patients (4.7%). Nineteen patients (11%) were categorized as having miscellaneous pathology, which included several patients with normal pancreatic tissue identified. The non-pancreatic contiguous and metastatic primary tumors necessitating distal pancreatectomy included liposarcoma (14 patients), gastrointestinal stromal tumor (11), leiomyosarcoma (6), gastric adenocarcinoma (4), ovarian cancer (3), and a variety of other primary tumors. Table 5 summarizes these results.

Complications

One hundred eight patients (63%) had no post-operative complications. The overall post-operative complication rate was 37%; 63 patients had one or more complications. The most common complications were pancreatic duct leak in 39 patients (23%), intraabdominal abscess in 13 patients (7.6%), new-onset insulin-dependent diabetes mellitus (IDDM) in six (3.5%), and portal vein thrombosis in three patients (1.8%). Ten patients (6%) required reoperation; the indications were small bowel obstruction (two patients), wound closure status post-trauma operation (2), small bowel perforation (1), gastroesophageal junction leak status post-subtotal gastrectomy (1), colon perforation (1), small bowel ischemia (1), necrotic stoma (1), and hemorrhage (1). Table 6 summarizes post-operative complications.

There were five deaths (2.9%) either in-hospital or within 30 days of operation. The causes of death included trauma from abdominal gun shot wound (1), intraabdominal hemorrhage (1), sepsis (1), and respiratory failure (2).

Table 3 Multivisceral Resections with Distal Pancreatectomy (n=75): 136 Organs/Tumors Resected (Exclusive of Spleen)

Organ/tissue	*N*	Additional organs/tumors resected
Stomach	29	Colon (10), adrenal (7), retroperitoneal tumor (7), kidney (6), small intestine (4), partial diaphragm (3), esophagus (2)
Colon	25	Retroperitoneal tumor (15), stomach (10), kidney (10), small intestine (10), adrenal (9), partial diaphragm (4)
Kidney	17	Retroperitoneal tumor (12), adrenal (11), colon (10), stomach (6), small intestine (6), partial diaphragm (4), lung wedge (1)
Adrenal	16	Kidney (11), retroperitoneal tumor (11), colon (9), stomach (7), small intestine (5), partial diaphragm (4), lung wedge (1)
Retroperitoneal tumor	16	Colon (15), kidney (12), small intestine (12), adrenal (11), stomach (7), partial diaphragm (5), lung (1)
Small intestine	14	Retroperitoneal tumor (12), colon (10), kidney (6), adrenal (5), stomach (4), partial diaphragm (3), lung wedge (1)
Liver (1 left hepatectomy, 8 non-anatomic wedge)	9	Partial diaphragm (1), lung wedge (1)
Diaphragm (partial)	6	Retroperitoneal tumor (5), colon (4), kidney (4), adrenal (4), stomach (3), small intestine (3), liver wedge (1), lunge wedge (1)
Esophagus	2	Liver wedge (1)
Lunge (wedge)	2	Liver wedge (1), retroperitoneal tumor (1), partial diaphragm (1), small intestine (1), kidney (1), adrenal (1)

Table 4 Final Pathology in 171 Patients Undergoing Distal Pancreatectomy

Pathology	Total number (%)	Group 1	Group 2
Contiguous/metastatic tumor from another organ	49 (29)	2	47
Mucinous cystadenoma	20 (12)	17	3
Chronic pancreatitis	19 (11)	14	5
Pancreatic adenocarcinoma	19 (11)	13	6
Neuroendocrine tumor	17 (9.9)	13	4
Serous cystadenoma	8 (4.7)	6	2
Intraductal papillary mucinous neoplasm	5 (2.9)	5	0
Solid pseudopapillary tumor	5 (2.9)	4	1
Pancreatic necrosis	5 (2.9)	3	2
Acinar cell carcinoma	3 (1.8)	2	1
Mucinous cystadenocarcinoma	2 (1.2)	2	0
Miscellaneous	19 (11)	15	4

Group 1=distal pancreatectomy +/− splenectomy; group 2=multivisceral resection

Fisher's exact test revealed that, when compared to patients undergoing standard distal pancreatectomy (group 1), those with a more extensive resection (group 2) including multiple viscera and/or metastatic or contiguous tumor resection had no significant difference in overall complication rate (35% v. 39%, $p=0.75$), leak rate (25% v. 20%, $p=0.47$), new-onset IDDM (3% v. 4%, $p=1.0$), and mortality (2% v. 4%, $p=0.656$) (see Table 7).

The incidence of pancreatic duct leak in relation to technique of pancreatic stump closure was 18% after suture closure, 18% after staple closure, and 33% after combined staples and suture closure.

Table 5 Non-pancreatic Contiguous and Metastatic Tumors Resected With Distal Pancreas

Primary tumor	Patients (%)
Liposarcoma	14 (29)
GIST	11 (22)
Leiomyosarcoma	6 (12)
Gastric adenocarcinoma	4 (8)
Ovarian cancer	3 (6)
Endometrial adenocarcinoma	2 (4)
Adrenal cortical adenoma	1 (2)
Esophageal adenocarcinoma	1 (2)
Mantle cell lymphoma	1 (2)
Colon adenocarcinoma	1 (2)
Malignant melanoma	1 (2)
Meningeal hemangiopericytoma	1 (2)
Renal cell cancer	1 (2)
Desmoid/spindle cell neoplasm	1 (2)
Total	49 (100)

Table 6 Post-operative Complications in 171 Distal Pancreatectomies

Complication	Number	%
Leak	39	23
Intraabdominal abscess	13	7.6
IDDM (new onset)	6	3.5
Portal vein thrombosis	3	1.8
Re-bleed	1	0.6
Cardiac arrest	1	0.6
DVT	1	0.6
Pulmonary embolus	1	0.6
Abdominal compartment syndrome	1	0.6
Reoperation	10	5.8
Death	5	2.9
LOS		
Mean	11±11 days	
Median	7 days	

Discussion

Our series of 171 patients who underwent distal pancreatectomy describes a high-volume single institution's experience with this procedure. This series is unique in the high number of patients (30%) who underwent distal pancreatectomy as part of an en bloc resection of contiguous tumor or for metastatic disease. Though infrequently an indication for distal pancreatectomy in other series, contiguous or metastatic disease was surprisingly the most common surgical indication in this cohort. Of these, liposarcoma and gastrointestinal stromal tumor (GIST) were the most common primary tumors. Other series have documented the most common indication for surgery as solid pancreatic neoplasm,[5,9] mucinous cystic neoplasm,[10] and chronic pancreatitis.[4] The overall complication rate was 37%, with pancreatic leak the most common complication. Compared with standard distal pancreatectomy, a more extensive resection had no greater complication rate.

Favorable morbidity and mortality has been cited in limited small series of patients with metastatic disease to the pancreas and with multivisceral resections involving pancreatectomy. In one series involving eight patients with

Table 7 Complication Rates: Standard Distal Pancreatectomy v. Extensive Resection

Complication	Standard distal pancreatectomy	Extensive resection	*p* value
Complication rate	35%	39%	0.75
Leak rate	25%	20%	0.47
New-onset IDDM	3%	4%	1.0
Mortality	2%	4%	0.656

pancreatectomy for metastatic tumors to the pancreas, primary tumors included colon carcinoma, renal cell carcinoma, duodenal leiomyosarcoma, and malignant fibrous histiocytoma.[8] In this group, average survival was 23 months although precise data on complications are not available for comparative purposes with the current study. Similarly, Pingpank et al.[7] detailed their experience with pancreatic resection for locally advanced primary and metastatic non-pancreatic neoplasms and found that median survival was 56 and 46 months, respectively. They advocate an aggressive surgical approach for the management of advanced intraabdominal malignancies, frequently requiring the resection of additional abdominal viscera, while stressing the importance of a margin-negative resection. Yao et al.[11] reviewed the records of 55 patients who were treated for primary gastrointestinal sarcomas and found that adjacent organ resection including distal pancreatectomy was required in 15 patients (27%) and that this did not adversely effect survival. It is agreed that negative margins remain the most important determinant of survival. In a recent large series, Kleeff et al.[12] suggested that multivisceral resections were associated with increased morbidity, particularly pancreatic fistula. The explanation for this observation is speculative, and was suggested to possibly relate to ischemia at the pancreatic stump margin.

The current study demonstrates a perioperative mortality rate of 2.9% and an overall post-operative complication rate of 37%, which is comparable to other series. Mortality rates from distal pancreatectomy have variously been reported as 0%,[5] 0%,[10] 0.9%,[1] 3.2%,[9] and 4%.[3] Recently, Rodriguez et al.[10] published a series of 66 patients who underwent distal pancreatectomy; overall post-operative morbidity was 52%, and 33% had complications directly related to pancreatic leak. Lillemoe et al.[1] analyzed 235 patients who underwent distal pancreatectomy and reported an overall post-operative complication rate of 31%; the most common complication was new-onset insulin-dependent diabetes (8%), and pancreatic fistula occurred in 5%.

Pancreatic stump leak, the most common complication in this series, occurred in 23% of patients who underwent a distal pancreatectomy. Of note, a meta-analysis including two randomized clinical trials and eight observational studies reported pancreatic fistula rates after distal pancreatectomy ranging from 0% to 61%.[4] Comparison of pancreatic leak or fistula rates between different series is difficult due to the lack of uniformity in defining this complication. The current study utilizes an internationally accepted definition of pancreatic leak that is relatively broad, including any patient with amylase-rich drain fluid that was 3× above normal serum levels at our institution. Fahy et al.[3] define leak as persistent drain output longer than 7 days or drain fluid amylase greater than 5,000 IU/l. Lillemoe et al.[1] did not precisely define pancreatic fistula. Sheehan et al.[5] defined pancreatic fistula as amylase-rich fluid in the drain after patients began a general diet. Knaebel et al.[4] notes that available studies use different concentrations of amylase in the fistula fluid, fluid amounts, methods of detection, and time points for description; some even omitted a definition. Going forward, the international study group definition and grading system should help standardize comparisons.[6]

Several groups have tried to ascertain the optimal method of pancreatic stump closure in order to reduce the frequency of pancreatic duct leak/fistula. In the current study, we found the incidence of pancreatic duct leak in relation to technique of pancreatic stump closure to be 18% after suture closure, 18% after staple closure, and 33% after combined staples and suture closure. Fisher's exact test revealed no significance difference in leak rate based on closure technique. Given this finding, and also because this study was not designed to compare closure techniques, we cannot recommend the optimal closure method.

One group found that the incidence of pancreatic fistula formation was not related to the method of closure of the pancreatic remnant (sewn v. stapled v. sewn and stapled) nor to the underlying pathologic process.[5] However, another group found that, although the method of closure of the pancreatic parenchyma had no effect on pancreatic leak rate, patients who had identification and direct ligation of the pancreatic duct had a significantly lower incidence of leak when compared to those who did not undergo pancreatic duct ligation (9.6% v. 34%, respectively, $p=0.001$). In addition, they did not find a significant association between pancreatic leak and pancreatic (versus non-pancreatic) pathology or contiguous organ resection.[9] Likewise, Fahy et al.[3] did not find a significant association between leak rate and method of pancreatic stump closure, presence of malignancy, or concomitant splenectomy. Meta-analysis of six studies failed to show a significant difference in leak rate when comparing stapled versus hand-sewn closure.[4]

Conclusion

In conclusion, this series demonstrates a wide variety of indications for distal pancreatectomy, with a unique experience in pancreatectomy for contiguous or metastatic tumor. Morbidity and mortality are comparable to that previously reported, even for more extensive or multivisceral resections. Patients with locally invasive or

metastatic disease to the pancreas may safely undergo distal pancreatectomy in an attempt to offer a palliative or survival benefit.

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J Gastrointest Surg (2008) 12:2183–2190
DOI 10.1007/s11605-008-0621-9

Pancreaticoduodenectomy with Vascular Resection for Local Advanced Pancreatic Head Cancer: A Single Center Retrospective Study

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Received: 20 May 2008 / Accepted: 15 July 2008 / Published online: 6 August 2008

Abstract
Introduction Pancreaticoduodenectomy with vascular resection remains a controversial approach for patients with local advanced pancreatic head cancer for the lack of evidences of survival and quality of life benefits. The aim of this study was to evaluate whether patients of pancreatic head cancer benefit on quality of life, survival, and treatment cost from pancreaticoduodenectomy with vascular resection compared with palliative therapy.
Materials and Methods Two hundred fourteen patients of pancreatic head cancer whose pancreatic head could not be dissected free from adjacent vascular were involved in this study. Eighty of these patients underwent pancreaticoduodenectomy with vascular resection, whereas other patients underwent palliative therapy.
Results Pancreaticoduodenectomy with artery resection offered worse outcomes on almost all aspects of quality of life and survival compared with palliative therapy. Pancreaticoduodenectomy with vein resection offered better 5-year survival compared with palliative therapy, whereas palliative therapy offered better quality of life after surgery.
Conclusion Pancreaticoduodenectomy with artery resection is nonsensical on treatment of pancreatic head cancer with artery adhesion/invasion. As for patients with vein adhesion/invasion, pancreaticoduodenectomy with vein resection should be performed cautiously. When actual vein invasion is very possible to have taken place, the choice of treatment strategy should be considered carefully by the pancreatic surgeons.

Keywords Pancreatic neoplasms · Neoplasm invasiveness · Pancreatectomy · Palliative care · Drug therapy · Brachytherapy

Introduction

Pancreatic cancer is lethal and is one of the leading causes of cancer death worldwide with rising incidence.[1] Despite of the advancement in its diagnosis and staging, little progress has been made in overall survival. The 5-year survival rate of patients is less than 5%, and the median survival is less than 1 year for the last three decades.[2–4]

Treatment of pancreatic cancer includes multiple modalities, but surgical resection offers the only potential chance for cure.[5] The first successful regional resection for a periampullary tumor was performed by Kausch in 1909 and was popularized by Whipple.[6] From 1980s, pancreaticoduodenectomy (PD) was performed extensively in large hospitals.[7,8] Unfortunately, because of the late diagnosis of the disease, 80–90% of patients are precluded from surgical resection for locally advanced or disseminated disease.[9] In patients with locally advanced disease, tumor adherence or invasion into adjacent structures, particularly the celiac and superior mesenteric vasculature, makes complete resection very difficult. To deal with vascular barriers, pancreatic surgeons performed en bloc resection with vein resection

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(portal vein, superior mesenteric vein, and superior mesenteric-portal vein confluence; Fortner type I operation) and artery resection (hepatic artery, superior mesenteric artery, and celiac artery; Fortner type II operation).[10] However, the extent of resection of pancreatic cancer is still under discussion.

In recent years at the Union Hospital, Wuhan, some patients of pancreatic head cancer with vascular adhesion/invasion being estimated to resectable were treated with PD with vein resection (VR) and/or artery resection (AR), and the others were treated with palliative therapy including surgical bypass, I125 brachytherapy, coeliac plexus block, and chemotherapy. We report herein the quality of life (QOL), the survival, and the economic outcomes of radical resection comparing with palliative therapy.

Materials and Methods

Patients

Nine hundred twenty-six patients with cancer of the pancreatic head were treated in Pancreatic Center, Union Hospital, Wuhan from January 1996 to December 2005. Excluding patients with disseminated disease (identified by preoperative imaging studies or surgical findings), severe medical comorbidities (oxygen-dependent obstructive pulmonary disease, unstable coronary artery disease, other malignancies, etc.), and Karnofsky Performance Status <40, 214 patients (23.1%) whose pancreatic head and uncinate process could not be dissected free from adjacent vascular were involved in this study. The details of these 214 patients were listed in Table 1. To determine the impact of vascular resection on postoperative complications, 247 patients of local advanced pancreatic head cancer who underwent PD without vascular resection formed the control group (PD group).

Table 1 Demographic Characteristics of 214 Patients of Pancreatic Head Cancer with Blood Vessel Adhesion/Invasion

	VR group (n=61)	VP group (n=89)	AR group (n=19)	AP group (n=45)
Age (median year, range)	52 (28–72)	53 (31–84)	46 (36–70)	58 (30–76)
Male (n, %)	38 (62.3)	50 (56.2)	15 (78.9)	32 (71.1)
Jaundice (n, %)	49 (80.3)	67 (75.3)	16 (84.2)	38 (84.4)
Abdominal pain (n, %)	32 (52.5)	43 (48.3)	11 (57.9)	27 (60.0)
Weight loss (n, %)	51 (83.6)	72 (80.9)	15 (78.9)	35 (77.7)

Preoperative Workup

Preoperative workup included history and physical examination, routine laboratory testing, chest radiography, electrocardiography, contrast-enhanced computed tomography (CT; 100%), magnetic resonance imaging (MRI/MRA/MRCP; 72.8%), and angiography (21.5%). Preoperative angiography was abandoned in 2000 with increasing accuracy of MRA and better vessel imaging of CT.

Treatment Strategy

Patients whose pancreatic head and uncinate process could not be dissected free from adjacent vascular undergoing radical resection or non-radical resection therapy depended on the extent of vascular adhesion/invasion according to preoperative imaging studies (mainly CT) and operative findings. Between January 1996 and June 2002, PD with VR was performed in patients whose portal vein (PV)/superior mesenteric vein (SMV)/superior mesenteric-portal vein confluence (SMPV) was adhered/invaded but not totally occluded, and PD with AR was performed in patients whose celiac axis (CA)/hepatic artery (HA)/superior mesenteric artery (SMA) was adhered/invaded but not stenosed. Between July 2002 and December 2005, with our preliminary findings that vascular resection (especially AR) played a little role in longer overall survival but worse QOL, the indication of vascular resection was limited. For vein invasion/adhesion, complete encircling of involved veins was also considered as a contraindication. PD with VR was only performed when tumor formed a convexity against the vein or tumor partially encircled the vein but the length of the involved vein was less then 5 cm. For artery invasion/adhesion, performance of AR was mainly according to the judgment of surgeons. AR was performed only when preoperative imaging studies or surgical findings indicated that actual invasion of artery have not taken place. Besides stenosis of the artery, fixation of surrounded lymph nodes, stiffness of surrounded lymphatic tissue and nerve plexus, and more than 5 cm of the length of the involved artery were also considered as the contraindications of PD with AR. Thus, part of the patients that were estimated to be resectable according to previous criteria were treated with palliative therapy. During these 10 years, 61 patients underwent PD with independent VR (without AR; VR group) and 19 patients underwent PD with AR (with or without VR; AR group). After surgery, patients were treated with systemic chemotherapy of gemcitabine (1,000 mg/m^2 on days 1, 8, and 15; every 4 weeks for one cycle) from 1999. Chemotherapies were started 4 weeks after radical resection except for postponed for sustained bone marrow suppression, and 36/80 patients completed all six cycles.

Palliative therapy was performed on 134 patients with vascular adhesion/invasion (89 with vein adhesion/invasion but not artery adhesion/invasion, VP group; 45 with artery adhesion/invasion with or without vein adhesion/invasion, AP group) who were not treated with radical resection. The unresectability of these patients, which was suggested by preoperative imaging, was confirmed by exploratory operation. Part of these patients were treated with biliary bypass (n=96) or gastric bypass (n=51) for treatment or prevention of jaundice or intestinal obstruction. Brachytherapy of I125 interstitial implantation and coeliac plexus block with alcohol were performed in all these patients. In addition, systemic chemotherapy of gemcitabine was performed. Chemotherapy was started 4 weeks after palliative surgery, except if postponed for sustained bone marrow suppression, and 70/134 patients completed all six cycles. Besides, biopsies were done in some of the patients for final diagnosis.

Assessment of Quality of Life

QOL assessment was initiated prior to surgery and completed at the 6-month follow-up. Patients were given questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, which were used to assess QOL in this study, before surgery (baseline) and 3 and 6 months after surgery (including PD with vascular resection, surgical bypass, I125 interstitial implantation, and coeliac plexus block).[11] The EORTC QLQ-C30 is a patient-based questionnaire that includes a total of 30 items and is composed of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), five single items assessing cancer symptoms (insomnia, dyspnea, appetite loss, constipation, and diarrhea), a global health assessment, and a question about perceived financial difficulties. Following the scoring instructions given by the EORTC Quality of Life Study group, the raw EORTC QLQ-C30 scores were linearly transformed to 0–100 scales before statistical analyses were performed. A higher score on functional scales and global health assessment represent a better level of functioning and QOL, whereas high scores on symptom scales and other single items represent more symptomatology. A mean change between 0 and 10 on the transformed scales was regarded as not clinically important; changes ≥10 were regarded as clinically significant, as previously described.[12]

Data Collection of Survival and Treatment Costs

Survival data were generated monthly by direct contact when patients underwent chemotherapy in Union Hospital, Wuhan and then every 3 month by telephone interview with the patient or his or her family until death or the end of data collection for this study (December 2007). The total treatment costs including charges of chemotherapy were calculated from office copies of payment receipts of patients from the treasurer's office, Union Hospital, Wuhan. Costs for treatment of complaints that were not concerned in pancreatic cancer (e.g. coronary heart disease, odontalgia, etc.) were excluded.

Statistical Analysis

All data analyses were performed using Statistical Package for the Social Sciences (SPSS) version 11.0 software. Analysis of variance was used to compare outcomes of patients treated with different strategies. All differences were considered significant at two-sided $P<0.05$. Data of QOL were analyzed for the subscales at each of the assessment points. The change in scores from baseline to each of the two given time points was calculated by subtracting the baseline score for each patient from the subsequent scores for the same patient. Treatment costs were described in terms of US Dollars with the exchange rate of 8.27 RMB yuan against 1 US dollar. Data of QOL and treatment costs were analyzed with analysis of variance (ANOVA)-Student–Newman–Keuls (SNK) test. Overall survival was demonstrated using the method of Kaplan and Meier, and log-rank test was used to evaluate differences between survival curves. One-, 2-, 3-, and 5-year survival were estimated by life tables.

Results

Pathological Findings

Surgical pathology demonstrated that the main pathological diagnosis of pancreatic head cancer was adenocarcinoma originating from pancreatic duct and bile duct and then was acinic cell carcinoma. Diagnoses of other carcinomas were rare. Actual vascular invasion was confirmed in 42 of 61 patients of VR group and 15 of 19 patients of AR group (Table 2).

Postoperative Course

Morbidity of postoperative complications, reoperation rate, and hospital stay of patients were shown in Table 3. Patients undergoing resection (VR group, AR group, and PD group) suffered a higher complication rate. Although VR was associated with thrombosis of PV and SMV, the overall complications of PD with VR were comparable with that of PD without VR (PD group). Compared with PD without AR (VR group and PD group), PD with AR demonstrated a higher complication rate. In addition, the

Table 2 Pathological Findings in All Four Groups

	VR group (n=61)	VP group (n=78)	AR group (n=19)	AP group (n=39)
Adenocarcinoma (n, %)	56 (91.8)	70 (90.0)	18 (94.7)	36 (92.3)
Acinic cell carcinoma (n, %)	3 (4.9)	3 (3.8)	1 (5.2)	2 (5.1)
Other carcinoma (n, %)	2 (3.3)	5 (6.4)	0 (0)	1 (2.6)
Actual blood vessels invasion (n, %)	42 (68.9)		15 (78.9)	

postoperative bleeding, which was the main complication associated with AR, increased the reoperation rate of PD with AR. Like postoperative complications, the median length of postoperative hospital stay after resection was longer than after palliation. Besides, results showed that AR prolonged the hospital stay of patients undergoing PD.

Quality of Life

Thirty-six of 61 patients in VR group, 78 of 89 patients in VP group, 12 of 19 patients in AR group, and 31 of 45 patients in AP group completed questionnaires of baseline and 3 month after surgery, 30 of 61 patients in VR group, 61 of 89 patients in VP group, five of 19 patients in AR group and 26 of 45 patients in AP group completed all three questionnaires. The changes in scores compared with baseline in representative aspects of QOL were shown in Fig. 1. Increased scores from baseline in Fig. 1a–c means improvement of global health status, physical functioning, and emotional functioning, while increased scores from baseline in Fig. 1d–f means worsening of pain, diarrhea, and economical impact.

Three months after surgery, VP and AP group demonstrated better global health status change than VR and AR group, respectively, although neither of the four groups showed clinical significance compared with baseline. In aspects of functional scales, patients undergoing palliative therapy (VP and AP group) worsened less in physical function, but patients undergoing radical resection (VR and AR group) obtained better emotional function. With respect to symptom scales and single items, patients undergoing palliative therapy benefited more than those undergoing radical resection in relief of pain and diarrhea. When compared with patients without artery adhesion/invasion (VR and VP group), patients with artery adhesion/invasion (AR and AP group) obtained comparable changes in scores in most items.

Six months after surgery, the differences of score changes in most items between VR and VP group leveled out, whereas the differences between AR and AP group widened. Patients in VR group improved in QOL but that in AR group worsened when compared 3 months after surgery.

In addition, according to the result of perceived financial difficulties, the treatment cost exercised severe adverse impact on economy in all groups.

Survival

Two hundred five of the 214 patients completed the follow-up until death, five of 214 patients (two in VR group and three in VP group) completed the follow-up at the end of data collection for this study, and four of 214 patients (one in VR group, two in VP group, and one in AP group) lost to follow-up were censored at the time of last contact. None of the 214 patients in this study died within 30 days of surgery, whereas one patient in AR group died 34 days after surgery for arterial thrombus formation. The median survival time for the VR, VP, AR, and AP group was 13, 12, 7, and 9 months, respectively. The estimated 1-, 2-, 3-

Table 3 Postoperative Course of Patients

	VR group (n=61)	VP group (n=78)	AR group (n=19)	AP group (n=39)	PD group (n=247)
Overall complications (n, %)	14 (22.9)	5 (6.4)	7 (36.8)	3 (7.7)	58 (23.5)
Wound infection (n, %)	2 (3.3)	2 (2.6)	0 (0)	1 (2.6)	8 (3.2)
Postoperative bleeding (n, %)	0 (0)	0 (0)	3 (15.8)	0 (0)	2 (0.8)
Intra-abdominal abscess (n, %)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)
Thrombosis (n, %)	2 (3.3)	0 (0)	1 (5.3)	0 (0)	0 (0)
Pancreatic fistula (n, %)	10 (16.4)	0 (0)	4 (21.1)	0 (0)	41 (16.6)
Biliary leak (n, %)	2 (3.3)	1 (1.3)	0 (0)	0 (0)	7 (2.8)
Colo-jejunal fistula (n, %)	0 (0)	1 (1.3)	0 (0)	1 (2.6)	1 (0.4)
Delayed gastric emptying (n, %)	0 (0)	1 (1.3)	1 (5.3)	1 (2.6)	4 (1.6)
Reoperation (n, %)	1 (1.6)	0 (0)	3 (15.8)	0 (0)	5 (2.0)
Postoperative hospital stay (days)	16±5	12±2	18±7	12±2	15±4

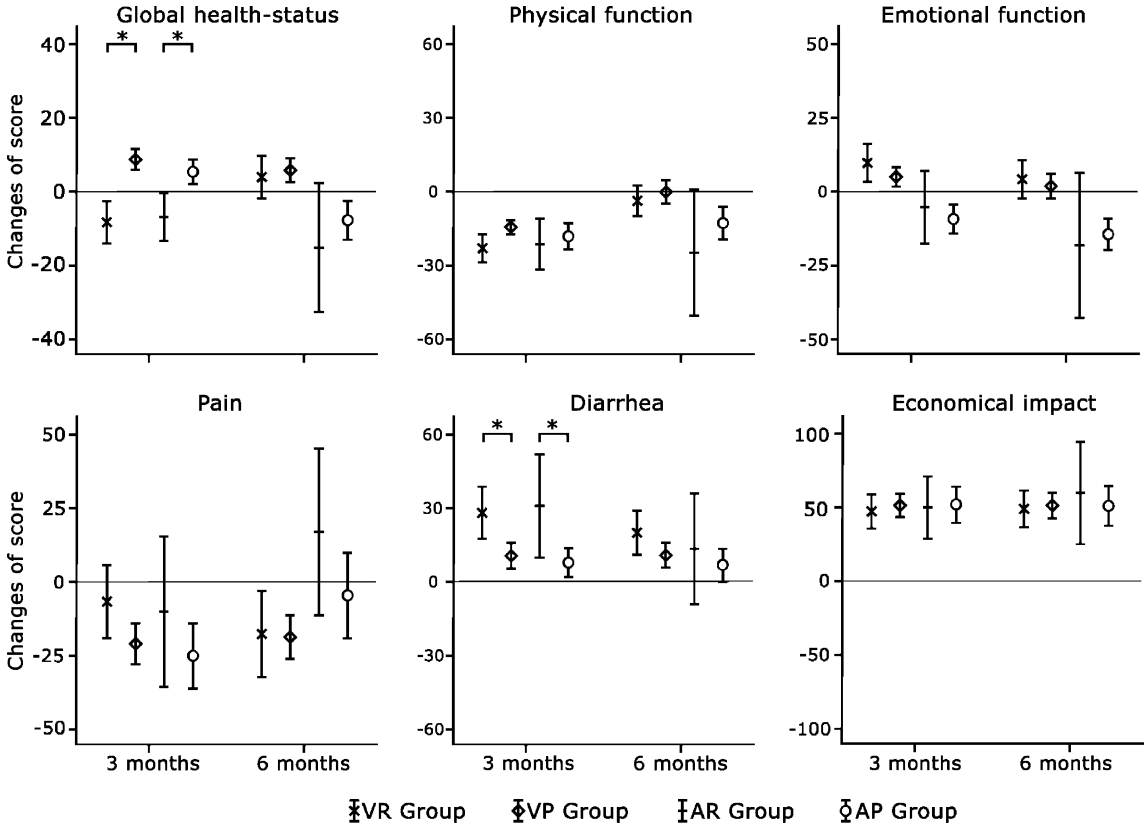

Figure 1 Changes in QLQ-C30 scores compared with baseline scores. Zero represents baseline. *Error bars* represent 95% confidence intervals of means of numerical changes in scores from baseline. *Error bars with positive values* represent improvement of functioning or worsen of symptoms. *Error bars with negative values* represent worsen of functioning or improvement of symptoms. *$P<0.05$.

and 5-year survival of all groups obtained with life tables were listed in Table 4. Survival analysis using the method of Kaplan and Meier among the four groups were displayed in Fig. 2. the difference between AR and AP group was statistically significant (log rank, $P=0.008$). Although there was no statistical significance in overall survival between VR group and VP group (log rank, $P=0.103$), the estimated 5-year survival of VR group were much higher than that of VP group.

To evaluate whether patients with actual invasion of veins benefit on survival from PD with VR, the survival of these patients was compared with that of patients undergoing palliation. Results showed that these patients acquired comparable survival with those undergoing palliation. None of these patients survived more than 5 years.

Treatment Costs

The treatment costs of the four groups were 15.8±2.8 thousands dollars (VR group), 14.1±4.3 thousands dollars (VP group), 17.2±6.7 thousands dollars (AR group), and 13.7±2.8 thousands dollars (AP group), respectively. There was no statistical significance among the four groups according to ANOVA-SNK test.

Discussion

More than three decades ago, PD was associated with a high perioperative mortality up to 25%; thus, few PD were performed for the treatment of pancreatic diseases. In recent

Table 4 One, 2, 3 and 5-Year Survival in All Four Groups

	1-year survival (M±SE)	2-year survival (M±SE)	3-year survival (M±SE)	5-year survival (M±SE)
VR Group	56%±6%	24%±6%	19%±5%	13%±4%
VP Group	52%±5%	23%±4%	11%±3%	1%±1%
AR Group	16%±8%	0%		
AP Group	40%±7%		10%±5%	0%

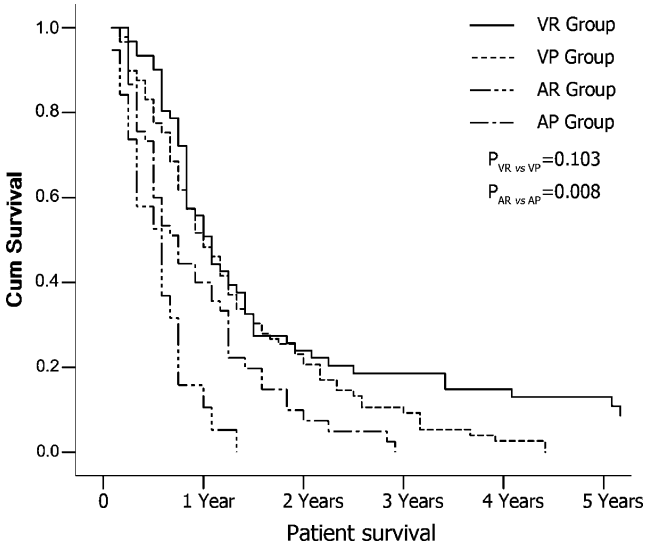

Figure 2 Kaplan–Meier survival curve for all four study groups.

years, with advances in surgical technique and perioperative care, the perioperative mortality had decreased to below 5% in high-volume centers. Thus, PD was performed frequently by surgeons.[7,8] Despite of this fact, only a small percentage of patients with pancreatic cancer were considered for PD because of the high morbidity of locally advanced and disseminated disease.

Because radical resection remains the only potential curative treatment for carcinoma of the pancreas, many surgeons sought to perform more radical resections to broaden indications of PD. To deal with vascular adhesion/invasion, which is frequently a limiting factor for radical resection, surgeons attempted to perform PD with infiltrated vascular resection. The first VR was reported by Moore in 1951, then Fortner further defined the concept of en bloc pancreatectomy in 1973.[10,13] Fortner reasoned that tumor infiltration to adjacent vessels, which was regarded as a contraindication of PD, could be overcome by en bloc resection of involved veins (type 1 resection) and arteries (type 2 resection). In recent years, experiences performing this radical procedure with VR increased. It has been reported to be performed with acceptable perioperative mortality comparably to PD without VR from many centers, but PD with VR remains a controversial approach because of the lack of evidence of survival and QOL benefit.[14–22] As for artery adhesion/invasion, it is regarded as a contraindication of PD by almost all surgeons because of high perioperative mortality and morbidity of complications.[23,24]

Our study reached an identical conclusion with previous studies on AR that it made no sense on patients with arteries adhesion/invasion. Most of patients undergoing PD with AR benefited neither on QOL nor on long-term survival. Although the perioperative mortality could be as low as 0% with increase of surgeon experience and advance in perioperative care, the morbidity of complications of PD with AR was much higher than non-radical resection therapy. More importantly, the estimated 1-year survival of patients undergoing PD with AR was only 16%±8%. The benefit of long-term survival for vascular resection with PD may be due to adherence to vasculature without actual invasion. Dismayingly, pathology of surgical specimens confirmed actual artery invasion in 78.9% patients in AR group. The high incidence of actual invasion may be due to the fact that arteries are surrounded by lymphatic tissue and nerve plexus, and tumor spread within these tissues is almost certain in case of actual artery invasion. In addition, the radical surgery procedure should also play a negative impact role in patients when actual invasion have taken place. Thus, artery adhesion/invasion was considered as a contraindication of PD in most cases in our hospital since July 2002.

Although experiences of PD with VR have been reported by many surgeons, there remains no consensus on its indications. In our institution, the judgment of resectability was mainly based on the degree of vein invasion.[25,26] We took up a relative radical position on PD with VR before June 2002, whereas PD with VR was performed more selectively after July 2002. The reasons were that (1) little obvious benefit on survival but damage in QOL was obtained from this radical resection according to experience from 1995 in our center and (2) only patients without actual vein invasion benefited on survival from PD with VR (Fig. 3), but actual vein invasion took place in more than two thirds of the patients estimated as "resectable" (Table 2). Therefore, many patients that can be estimated to resectable with radical position were treated with palliative therapy. In

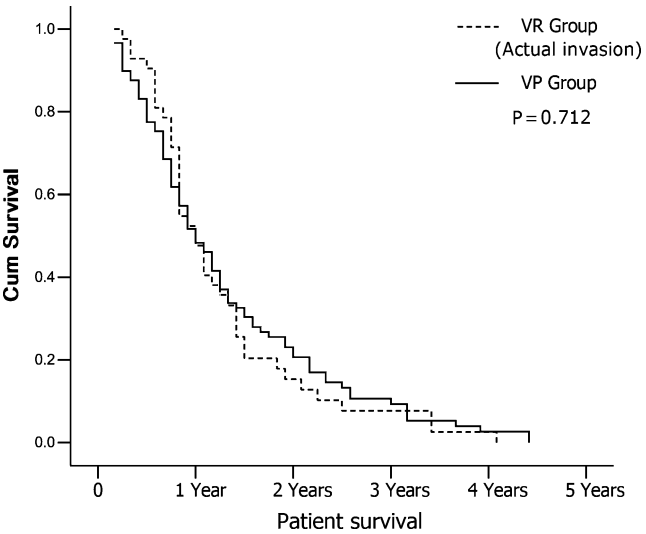

Figure 3 Kaplan–Meier survival curve for patients with actual invasion of veins in VR group and all patients in VP group.

review of all patients with vein adhesion/invasion of 10 years in our center, palliative therapy offered comparable 1- and 2-year survival with advances in chemotherapy, but PD with VR offered better 5-year survival. In spite of this, it must be pointed out that, besides treatment strategy, there are other important factors contributing to patient survival. Patients in VP group were mainly estimated unresectable, whereas patients in VR group were all estimated respectable; thus, VP group should be worse than VR group in tumor grade, tumor size, etc. Considering these factors, the difference of the effect on patient survival between PD with VR and palliative therapy should be smaller than shown. Thus, randomized controlled trial is needed for further study on the comprehensive evaluation of different treatment strategies.

QOL is another criterion for treatment strategy of pancreatic cancer. QOL of patients undergoing palliative therapy increased to preoperative levels more quickly than that of patients undergoing PD with VR after surgery. Six months after surgery, patients undergoing PD with VR and palliative therapy scored comparably in most items. With respect to pain assessment, patients undergoing palliative therapy scored better than patients undergoing PD with VR 3 months after surgery, which confirmed the favorable effect of coeliac plexus block. With respect to diarrhea assessment, for the skeletonization of common hepatic artery, celiac axis, and superior mesenteric artery in PD with VR and the coeliac plexus block in palliative therapy, postoperative diarrhea developed in both group but that of VR group were more serious than VP group. Six months after surgery, a few patients in VR group still suffered severe diarrhea. Based on the assessment of financial difficulties, the treatment costs of pancreatic cancer were big burden for Chinese patients and played severe adverse impact on economy, and the impact of both treatment strategies were equal. Considering the difference of the morbidity of postoperative complication and the length of hospital stay between patients undergoing resection and palliation, we tentatively put forward that PD procedure plays an important role in the deterioration of postoperative QOL. However, although results showed that the morbidity of postoperative complication and the length of hospital were comparable between patients undergoing PD with VR and PD only, this study has a limitation on the evaluation of the impact of VR procedure on postoperative QOL for the lack of the QOL assessment of patients undergoing PD only.

Conclusion

Our results showed that, in most cases, patients can benefit neither on QOL nor on long-term survival from PD with AR; thus, PD with AR should be performed in exceptional circumstances only. As for patients with vein adhesion/invasion, systematic palliative therapy offered better QOL and comparable 1- and 2-year survival, whereas PD with VR offered better 5-year survival. However, for the differences of tumor grade, tumor size, etc. of the PD group and VP groups, the benefit of PD with VR on survival is ambiguous. Thus PD with VR should be performed restrainedly. Because no preoperative examinations can distinguish actual invasion form inflammatory infiltration to date, surgeons must evaluate the possibility of actual vein invasion according to their experiences. When preoperative imaging studies or surgical findings indicate that actual vein invasion is very possible to have taken place, the choice of treatment strategies should be considered carefully by the pancreatic surgeons.

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J Gastrointest Surg (2008) 12:2191–2195
DOI 10.1007/s11605-008-0593-9

Clinicopathological Feature and Surgical Outcome of Choledochal Cyst in Different Age Groups: The Implication of Surgical Timing

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Received: 30 January 2008 / Accepted: 25 June 2008 / Published online: 2 August 2008

Abstract
Background/aims Surgical resection of choledochal cysts (CC) has become standard treatment. However, surgery is not universally recommended in early infancy and/or asymptomatic patients. In order to investigate the optimal timing of CC excision, we analyzed clinicopathological data and surgical results from different age groups.
Material and methods This retrospective review included 107 patients (77 females, 30 males) who underwent CC resection at the National Taiwan University Hospital between January 1988 and December 2005. Patient demographic, clinical, and surgical data were collected and analyzed.
Results The patients were divided into three groups according to age at the time of surgery: <1 year old (group I, n=26), 1−16 years old (group II, n=48), and >16 years old (group III, n=33). About two thirds of the patients in group I had jaundice, while abdominal pain related to inflammation was the commonest symptom in groups II and III. Group I suffered significantly fewer surgical complications and less severe liver fibrosis than groups II or III.
Conclusion CC surgery in infancy and in asymptomatic patients is safe and may prevent the complications of this condition. The results support a recommendation for early excision.

Keywords Choledochal cyst · Surgery · Infant

Introduction

Choledochal cysts (CC) are more common in the Far East than in populations of Western European origin,[1,2] with a higher incidence in female patients.[3] Clinical presentation varies greatly according to race and age.[2,4] Right upper quadrant pain, jaundice, and a mass were once considered a classic triad but this is rarely seen now. Modern imaging techniques facilitate correct diagnosis from the antenatal period to adult life, resulting in more and more patients being diagnosed before symptoms appear.[5]

The most commonly used classification describes five types of CC.[6,7] Type I is the most common and refers to dilatation of the common bile duct, which can be cystic, focal, or fusiform. Type IV is the second most common and involves dilatation of both the intrahepatic and extrahepatic biliary trees. Whatever the type, complete excision and hepaticojejunostomy is the standard management where possible. Our previous report, as well as several other studies, proposed that the timing of surgery should be early after diagnosis to reduce the incidence of complications and, in particular, to prevent liver damage in neonates.[8,9] However, relatively little information about the clinicopathological features and surgical outcomes in different age groups is available. We, therefore, analyzed our patients' data and correlated the findings to the optimal surgical timing.

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Table 1 The Clinical Manifestations in Each Group

Symptoms	Group		
	I (n=26)	II (n=48)	III (n=33)
Jaundice	17 (65.4%)	16 (33.3%)*	12 (36.4%)*
Pain	1 (3.8%)	24 (50.0%)*	27 (81.8%)**
Mass	9 (34.6%)	11 (22.9%)*	6 (18.2%)*
Pancreatitis	2 (7.7%)	23 (47.9%)*	18 (54.5%)*
Classical triad	0	6 (12.5%)	2 (6.1%)
No symptoms	6 (23.1%)	8 (16.7%)	3 (9.1%)

*p<0.05 (vs. group I); **p<0.05 (vs. group II)

Materials and Methods

Patient Population

This retrospective review included 107 patients (77 females, 30 males) who underwent CC resection at the National Taiwan University Hospital between January 1988 and December 2005. Their ages ranged from 5 days to 64 years. In six patients, CC was diagnosed prenatally, and all of these patients were operated on within 30 days of birth.

The patients were divided into three groups according to age at the time of their operation: <1 year old (group I, n=26), 1−16 years old (group II, n=48), and >16 years old (group III, n=33). The patients operated on before 1996 accounted for roughly half of our patients (57 of 107 patients). The patients operated on before 1996 made up 53% of the group I patients (14/26), 58.3% of the group II patients (28/48), and 45.5% of the group III patients, respectively. All patients underwent cyst excision and Roux-en-Y hepaticojejunostomy. In order to evaluate the grade of portal fibrosis, a liver biopsy specimen was taken during the excision.

Table 2 Serum Levels of Liver and Pancreas Function Markers in Each Group

	I (n=26)	II (n=48)	III (n=33)
Bilirubin (mg/dL)			
Total	6.57±2.12	3.21±1.33*	2.80±1.01*
Direct	3.46±1.45	1.91±0.62*	1.73±0.63*
AST (IU/L)	109±30	115±37	94±29
ALT (IU/L)	67±21	129±41*	133±37*
ALP (IU/L)	255±60	657±141*	687±104*
γ-GT (IU/L)	53±10	166±44*	183±50*
Amylase (IU/L)	155±57	387±141*	461±143*
Lipase (IU/L)	234±80	464±150*	493±161*

AST Aspartate aminotransferase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *γ-GT* gamma-glutamyl transpeptidase
*p<0.05 (vs. group I)

Data Collection and Statistical Analysis

Data were retrieved from each patient's medical records, including demographic information, clinical presentations, surgical information, histopathological results, and hospital course. Complications within 30 days of surgery or during the same hospitalization were considered to be surgical morbidities. Long-term outcome was obtained through clinical follow-up or contact with the patient and, if necessary, family members. Continuous data are presented as means±standard deviation. The Mann–Whitney U test, Pearson chi-square test, and Fisher's exact test were used where applicable. Significance was set at p<0.05.

Results

Each group varied significantly in terms of clinical manifestations. About two thirds of patients in group I had jaundice, while abdominal pain related to inflammation was the commonest symptom in groups II and III (Table 1). A greater proportion of groups II and III had symptoms of pancreatitis compared to group I (Table 1). Laboratory testing reflected the difference in clinical symptoms and signs. Group I had a significantly higher mean serum bilirubin than groups II and III, and serum liver and pancreatic enzymes were, on average, lower in group I than the other groups (Table 2). A minority of patients, however, were completely free from clinical symptoms/signs on diagnosis. In these patients, CC was diagnosed incidentally during prenatal ultrasonography or abdominal ultrasonography performed for other medical reasons, such as hepatitis or hepatic tumor screening.

Almost all patients had type I CC, only five patients (4.7%) had type IV, and no other types were present. The average duration of surgery was significantly shorter in group I compared to the other groups (Table 3). A greater proportion of patients in groups II and III had high amylase levels in their bile and bile sludge than in group I (Table 3), indicating that these groups had suffered more severe cholangitis. One patient in group I had a spontaneous perforation of CC, resulting in bile peritonitis and emergency surgery before recovering well.

Histopathological examination showed that the proportion of choledochal cystic inflammation and cholecystitis was significantly greater in groups II and III than I (Table 4). Liver biopsy was performed in 26 group I patients (100%), 40 group II patients (83.3%), and 16 patients group III patients (47.1%) in order to evaluate the grade of liver fibrosis, which was significantly more severe in groups II and III. No malignancies were identified.

In total, there were 16 complications. These included wound infection, bile leakage, subhepatic abscess, ileus due

Table 3 Image and Surgical Findings in Each Group

	I (n=26)	II (n=48)	III (n=33)
Type I	26	46	30
Type IV	0	2	3
Surgical duration (min)	126±20	162±35*	178±31*
Anomalous pancreatobiliary union channel[a]	–	15/31 (48.4%)	7/15 (46.7%)
Pancreatic duct dilatation[b]	0	3 (6.3%)	0
High amylase in bile[a]	5/20 (25%)	33/43 (76.7%)*	18/21 (85.7%)*
Bile sludge/stones	4 (15.4%)	18 (37.5%) *	17 (51.5%) **
Accessory hepatic duct	0	2 (4.2%)	0
Spontaneous perforation	1 (3.8%)	0	0

*p<0.05 (vs. group I); **p<0.05 (vs. group II)
[a] The item not checked in all patients. The data were presented as "number of positive finding/number of measured patients." Number in the parenthesis is percentage of measured patients.
[b] Detected by magnetic resonance cholangiopancreatography

to adhesion, and intraperitoneal hemorrhage (Table 5). Two patients required reoperation, and both patients subsequently did well. There was no surgery-related mortality. There was a significant difference in the complication rates of the groups (7.7% in group I, 12.5% in group II, and 24.2% in group III; p<0.05), but not in the duration of postoperative hospitalization (10.6±3.9, 9.2±3.9, and 9.0±3.2 days in groups I, II, and III, respectively).

Discussion

Although the precise etiology of CC remains unclear, there is a well-established association between CC and biliary malignancy, especially cholangiocarcinoma. The incidence of malignancy ranges from 10% to 30%.[10–15] Complete cystic excision with hepaticoenterostomy is the standard surgical strategy because it lowers the risk of malignancy arising from the residual cyst. However, there is a lack of consensus about the optimal timing of surgery. Our previous report and other studies advocated for surgery early after diagnosis: this

Table 4 The Histopathological Results

	I (n=26)	II (n=48)	III (n=33)
Cholecystitis	6 (23.1)	31 (64.6)*	21 (63.6)*
Cystic wall inflammation	8 (30.8)	31 (64.6)*	31 (93.9)**
Portal fibrosis[a]	7/26 (26.9%)	16/40 (40.0%)*	14/16(87.5%)**

*p<0.05 (vs. group I); **p<0.05 (vs. group II)
[a] The item not checked in all patients. The data were presented as "number of positive finding/number of measured patients." Number in the parenthesis is percentage of measured patients.

Table 5 Postoperative Complications and Course

Group	I (n=26)	II (n=48)	III (n=33)
Complications	2 (7.7%)	6 (12.5%)*	8 (24.2%)**
Bile leakage	1	1	1[a]
Subhepatic abscess	0	1	2
Adhesion ileus	1	2	2
Intraperitoneal hemorrhage	0	1[a]	0
Wound infection	0	1	3
Postoperative hospitalization (days)	10.6±3.9	9.2±3.9	9.0±3.2

*p<0.05 (vs. group I); **p<0.05 (vs. group II)
[a] Reoperation was needed

reduces the risk of postoperative complications[9,16] and liver portal fibrosis.[8] In the present study, we analyzed the clinicopathological data of patients undergoing surgery at different ages and compared the surgical results. Patients operated on at older ages had more severe symptoms related to cystic inflammation and more postoperative complications. We, therefore, propose that CC should be managed surgically as soon as possible after diagnosis.

Because of improvements in diagnostic imaging, a correct diagnosis of CC can be made in the early stages of the disease and even prenatally.[17] Six patients in group I (23.1%) were diagnosed prenatally by ultrasonography and subsequently underwent surgery within 30 days of birth. None of these patients had surgical mortality or morbidity. Lee et al. reported similar results, with no complications occurring in patients undergoing surgery before the 30th postnatal day.[9] Together, these findings suggest that surgery for CC is safe and feasible in patients diagnosed prenatally. Though there is still a lack of evidence regarding the optimal timing of surgery, we believe that the surgery and accompanying general anesthesia would be best tolerated about 1 month after birth.

Less severe local inflammation is one of the reasons why surgery for CC is even easier and safer in the early infancy than in the older patients. Local inflammation usually results in distortion of the anatomy due to adhesions of the nearby structures, increased bleeding during dissection, and poorer healing of the anastomosis. Since the severity of cholangitis and pancreatitis intensifies as the patient becomes older, early surgical intervention, therefore, not only prevents the possible complication of inflammation but also reduces the difficulty of operation.

In agreement with previous reports,[4] our series revealed that neonates and infants with CC frequently exhibited jaundice, while pancreatitis and cholangitis were more common in the older patients. It has been proposed that obstructive cholangiopathy is the main pathology in neonates with CC. However, free reflux of pancreatic juice into the choledochus, resulting in acute and chronic cholangitis

with abdominal pain, was the major underlying etiology for the older patients' symptoms. Though the pathophysiological mechanisms are different at different ages, either obstructive cholangiopathy or reflux of pancreatic juice can contribute to liver fibrosis. Liver biopsy showed portal fibrosis in a substantial percentage of all the patient groups in our series, and the severity of the liver fibrosis increased with age (Table 4). Prompt surgery may prevent and even improve liver fibrosis.[18]

Long-standing reflux of pancreatic juice may contribute to chronic inflammation and subsequent carcinogenesis of the biliary trees. Acute complications of choledochal cysts—pancreatitis, cholangitis, and obstructive jaundice—are contraindications to corrective surgery and are reported in approximately 15% of patients.[19] We suggest that surgery should be performed after the acute inflammation subsides. There are two reasons for this: (i) infection can usually be controlled by intravenous antibiotics and nonsurgical modalities, such as endoscopic interventions[20] and (ii) local acute inflammation in the portal area may hinder surgery and increase the risk of surgical complications. In a previous report, definitive surgery was performed after a median interval of 10 days (range 7±68 days) after successful endoscopic retrograde cholangiopancreatographic intervention.[20]

One of the 107 patients in our series had a spontaneous perforation of the CC. The incidence of this complication has been reported to be as high as 7%.[21] Though the etiology is still debated, several possible mechanisms have been suggested, including congenital weakness of the bile duct wall, bile flow obstruction, and pancreatic juice reflux. The risk of spontaneous perforation and consequent bile peritonitis is another reason for early excision of CC in asymptomatic patients.

In the present study, none of the patients had a malignant change in the CC found during the pathological examination. However, the incidence of malignant change ranges from 8% to 19% in the Asian literature,[22–24] with similar figures in some Western series.[25,26] Our policy of prompt surgical intervention and the younger patient population in our study may explain why cholangiocarcinoma was not encountered. Moreover, patients treated by means of the cystic drainage procedure carry an increased risk of malignant change.[19,23,25] We, therefore, in agreement with other reports, advocate complete cyst excision in these patients.

Our study had a number of limitations. First, our results were based on cross-sectional retrospective data, so we were unable to ascertain whether the incidence of complications is higher when CCs are left unexcised. Second, our study was based on a relatively small sample from a single medical center, so it is unclear whether the results are generalizable to other medical settings. Third, the entire study period lasted 17 years. It is important to consider the influences on surgical outcomes of improvements in medical techniques that occurred during this period. In particular, all six patients prenatally diagnosed with CC were operated on after 1996 (in the last 8 years of the study period), when ultrasonography began to be widely used as a prenatal screening tool. The discrepant distribution of our patients according to surgical period may have led to some bias in interpretation of our data.

Conclusion

In summary, CCs manifest differently at different ages. The risk of preoperative inflammation and complications, such as cholangitis, pancreatitis, and liver fibrosis, increase with age. Moreover, surgery in the neonatal period is safe and may prevent these complications. Our findings, therefore, support a recommendation for early excision of CC, even in asymptomatic patients and including in the early infancy.

Acknowledgement This work was supported by the institutional grants from National Taiwan University Hospital 97-N-1006 and National Taiwan University Hospital Yun-Lin Branch 96-N-017.

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J Gastrointest Surg (2008) 12:2196–2203
DOI 10.1007/s11605-008-0563-2

The Survival Paradox of Elderly Patients After Major Liver Resections

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Received: 15 January 2008 / Accepted: 4 June 2008 / Published online: 24 July 2008

Abstract
Objective The objective of this study is to assess the outcome of liver resections in the elderly in a matched control analysis.
Patients and Methods From a prospective single center database of 628 patients, 132 patients were aged 60 years or over and underwent a primary major liver resection. Of these patients, 93 could be matched one-to-one with a control patient, aged less than 60 years, with the same diagnosis and the same type of liver resection. The mean age difference was 16.7 years.
Results Patients over 60 years of age had a significantly higher American Society of Anaesthesiologists (ASA) grade. All other demographics and operative characteristics were not different. In-hospital mortality and morbidity were higher in the patients over 60 years of age (11% versus 2%, $p=0.017$ and 47% versus 31%, $p=0.024$). One-, 3-, and 5-year survival rates in the patients over 60 years of age were 81%, 58%, and 42%, respectively, compared to 90%, 59%, and 42% in the control patients ($p=0.558$). Unified model Cox regression analysis showed that resection margin status (hazard ratio 2.51) and ASA grade (hazard ratio 2.26), and not age, were determining factors for survival.
Conclusion This finding underlines the important fact that in patient selection for major liver resections, ASA grade is more important than patient age.

Keywords Liver · Surgery · Aged · Survival · Case-control studies

Introduction

Liver resection is the preferred treatment for a wide range of primary and secondary liver tumors. Advances in preoperative assessment, surgical techniques, anesthesiology, and postoperative care have progressively lowered the perioperative risk of liver resections and thereby widened operative indications.[1–3] This has markedly increased the number of patients evaluated for liver resections.[4]

Besides this, increased life expectancy and improved general health status lead to an increase in the number of elderly patients eligible for liver resection.

These developments stress the need to determine the influence of advanced age on the outcome after liver resection. Age-associated decline in liver volume, hepatic blood flow, and regenerative capacity might be responsible for higher risks associated with liver resections in elderly patients.[5] Nevertheless, several observational cohort studies addressed this issue and have failed to show age to be an independent risk factor influencing short- and long-term survival after liver resections.[6–11] These observational

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cohort studies included a mix of wedge, minor, and major liver resections, and retrospectively compared study groups based on patient age at the time of liver resection. This study design may include a selection bias in terms of diagnosis and magnitude of liver resection.

The aim of this study is to assess the short- and long-term outcome of liver resections in the elderly in a matched control analysis. In order to address the shortcomings of the earlier mentioned studies, a homogeneous cohort of patients undergoing major liver resections for primary or secondary tumors in otherwise normal liver parenchyma was chosen.

Patients and Methods

Between December 1978 and December 2006, 628 consecutive patients underwent a primary liver resection in our institution. Their medical data were collected in a database. The patient variables included patient demographics, operative data, pathology data, and follow-up data concerning morbidity and survival. Follow-up was completed until December 31, 2006.

From this database, 236 patients (37.6%) were over the age of 60 at the time of liver resection. Of these patients, 74 underwent a resection of less then three Couinaud's segments[12] and were therefore excluded. A further 30 patients, treated for Klatskin tumors, were also excluded as this aggressive type of tumor tends to result in a different short- and long-term outcome compared to other primary or secondary hepatic malignancies.[13,14] Another argument to exclude patients treated for Klatskin tumors was the prolonged preoperative cholestasis resulting in parenchymal changes.

Therefore, the study group consisted of the remaining 132 patients over 60 years of age. Of these patients, 93 could be matched with a control group of patients aged less than 60 years at the time of liver resection. Patients were matched on a one-to-one basis with control patients with the same type of tumor and the same type of liver resection according to Couinaud segments. In case of more than one potential match, the control patient who underwent the liver resection at a date closest to the operation date of the match was selected in order to minimize any potential historical bias. All included patients had non-cirrhotic parenchyma.

An exact match could not be found for 39 patients. The demographic data of these 39 unmatched patients were compared with the data of the matched patients to assess a potential selection bias.

Data about pre- and postoperative treatment protocols and techniques of liver resections have been published in earlier reports by this group.[13,15]

Study Variables

Study variables were age, gender, American Society of Anaesthesiologists (ASA) score, type of tumor, type of resection, intraoperative blood transfusions, and resection margin status. Type of tumor was divided in colorectal metastasis, hepatocellular carcinoma, or other malignant or benign tumors. In concordance with recent literature,[10] intraoperative blood transfusions were noted as less than three packed cells or three or more packed cells transfused peroperatively. Resection margin status was defined as R0 resection when all surgical margins were microscopically free of tumor cells, R1 resection when tumor cells were identified on light microscopy in one or more of the margins, and palliative resection when macroscopic tumor was left behind in one or more of the margins or outside the liver. R0 resections were considered radical, and R1 and palliative resections were considered irradical.

Outcome Parameters

Outcome parameters were patient survival, disease-free survival, in-hospital mortality, and postoperative morbidity and reinterventions. Patients with benign tumors and patients with palliative resections were excluded when computing disease-free survival. Patient survival was defined as time between the operation date and the date of patient death. Surviving patients at the end of the study period were censored. Disease-free survival was defined as the time between the operation date and the date of tumor recurrence. Recurrence was proven histological by imaging studies or by compelling clinical suspicion. Patients without evidence for recurrence were censored after the end of the study period. Mortality was defined as in hospital mortality during the initial hospitalization for the liver resection. Postoperative morbidity was assessed by analyzing the incidence of bleeding, hepatic, biliary, lung, wound, and infectious complications. Postoperative morbidity was expressed as the proportion of patients with any of these complications. The length of postoperative intensive care unit (ICU) stay, as well as the length of hospital stay, was recorded.

Study Design and Statistical Methods

In order to assess differences in baseline characteristics between the matched patients and the control patients, study variables were compared. Since not all patients over 60 years of age could be matched, a potential selection bias existed. Therefore, the 93 matched patients and the 39

unmatched patients were also compared. To assess a potential historical bias, the difference in operation date between the matched patients and the control patients was assessed.

In order to assess differences in outcome between the matched patients and the control patients, outcome parameters were compared. The influence of the study variables on overall outcome was assessed in a univariate analysis in a unified model of matched and control patients. Parameters with a p value <0.10 as well as age, being the parameter of paramount interest in this study, were entered into a Cox regression analysis in a backward likelihood manner for multivariate analysis.

Categorical and continuous variables were compared using the Pearson chi-square test and the Mann–Whitney U test where appropriate. Survival analyses were performed by the Kaplan–Meier method, and comparisons were made using the log-rank test.[16] A significant difference was defined as a p value <0.05.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 14.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Demographics

Patient demographics and operative characteristics are shown in Table 1. Mean age difference between the matched and the control patients was 16.7 years (SD, 9.2 years). The operation date of the matched patients was on average 1.2 years (SD, 3.4 years) later, compared to the operation date of the control patients. The difference between operation dates was below 5 years for 95% of the matches.

As expected, significant differences between the matched and the control patients were found regarding age but also regarding ASA status $p<0.001$. Since only two patients were ASA grade 4, grades 3 and 4 were combined in one group. Of the matched patients, 24% were ASA grade 3 or 4 versus 8% of the control patients. Of the control patients, 49% were ASA grade 1 versus 22% of the matched patients.

Significant differences between the matched and the unmatched patients were found regarding the type of tumor

Table 1 Patient Demographics and Operative Characteristics

	Matched elderly, n=93	Control group, n=93	p value matched versus control	Unmatched elderly, n=39	p value matched versus unmatched
Median age range, years	66 (60–82)	52 (19–59)	<0.001[a]	68 (61–78)	n.s.[a]
Gender, n %					
Male	49 (53)	55 (59)	n.s.[a]	24 (62)	n.s.[a]
ASA grade, n %			<0.001[b]		n.s.[b]
Grade 1	21 (23)	47 (51)		11 (28)	
Grade 2	48 (52)	39 (42)		15 (39)	
Grade 3 or 4	24 (26)	7 (8)		12 (31)	
Type of disease			n.s.[b]		0.010[b]
Colorectal metastasis	70 (75)	70 (75)		25 (64)	
Hepatocellular Carcinoma	15 (16)	15 (16)		3 (8)	
Other malignant disease	3 (3)	3 (3)		7 (18)	
Benign disease	5 (5)	5 (5)		4 (10)	
Type of resection			n.s.[b]		0.002[b]
Right trisectionectomy S 4, 5, 6, 7, 8±1	19 (20)	19 (20)		4 (10)	
Left trisectionectomy S 2, 3, 4, 5, 8±1	4 (4)	4 (4)		1 (3)	
Left hemihepatecomy S 2, 3, 4±1	21 (23)	21 (23)		10 (26)	
Right hemihepatectomy S 5, 6, 7, 8±1	49 (53)	49 (53)		18 (46)	
Other 3 or more segments	0	0		6 (15)	
Resection margin status			n.s.[b]		n.s.[b]
R0	75 (81)	74 (80)		30 (77)	
R1 or R2	9 (10)	12 (13)		3 (8)	
Benign disease	5 (5)	5 (5)		4 (10)	
Missing	4 (4)	2 (2)		2 (5)	
Intraoperative blood transfusion			n.s.[a]		n.s.[a]
Three or more RBCs	29 (31)	24 (26)		9 (23)	

ASA American Society of Anaesthesiologists
[a] Pearson chi-square test
[b] Chi-square test

p=0.01. Of the matched patients, 16% had hepatocellular carcinoma HCC versus 8% of the unmatched patients. Of the unmatched patients, 18% had non-colorectal, non-HCC malignancies versus 3% of the matched patients. Gender, resection margin status and intraoperative blood transfusion were not significantly different between the matched patients and the unmatched patients.

Short-term Outcome

Matched Versus Control Patients

Short-term outcome parameters are shown in Table 2. In-hospital mortality was 6.5%. In-hospital mortality was significantly higher in the matched patients compared to the control patients 11% versus 2%, p=0.017. Four matched patients versus one of the control patients died because of sepsis. Four matched patients died because of liver insufficiency, compared to one of the control patients. One matched patient died of massive pulmonary embolism and another of pulmonary aspiration.

Unified Model Analysis

Patients with ASA grade 1, 2, or 3/4 had an in-hospital mortality rate of 2.5%, 6.9%, and 14%, respectively p=0.101. Gender, type of disease, type of resection, intraoperative blood transfusion, and resection margin status also showed no significant influence on in-hospital mortality.

Overall postoperative morbidity was 39%. Morbidity was significantly higher in the matched patients compared to the control patients 47% versus 31%, p=0.024. Morbidity was significantly higher after resections of five or more Couinaud segments compared to resections of three or four Couinaud segments 59% versus 33%, p=0.002, after three or more preoperative transfusions compared to less than three 53% versus 34%, p=0.017, and after radical resections compared to irradical resections 62% versus 38%, p=0.039. ASA grade, gender, and type of disease showed no significant influence on morbidity.

The overall reintervention rate was 22%. Overall median length of stay in the ICU and hospital were 1 range, 0–45, and 16 range, 5–116 days, respectively. The reintervention rate and length of stay in the ICU and hospital were not significantly different between the matched and the control patients. The reintervention rate was significantly higher in male patients compared to female patients 27% versus 15%, 0.043, in patients undergoing resection of five or more Couinaud segments compared to resections of three or four Couinaud segments 41% versus 15%, p<0.0005, and in patients with three or more intraoperative transfusions compared to patients with less than three 32% versus 17%, p=0.027. ASA grade, type of disease, and resection margin status showed no significant influence on morbidity.

Long-term Outcome

Matched Versus Control Patients

One-, 3-, and 5-year survival in the matched patients was 81%, 58%, and 42%, respectively. One-, 3-, and 5-year survival in the control patients was 90%, 59%, and 42%, respectively p=0.558; Fig. 1. At the end of the study period, 49 53% of the matched patients and 45 48% of the control patients were still alive.

Table 2 ICU/Hospital Stay, Mortality, and Morbidity

	Matched elderly, n=93	Control group, n=93	p value[a] matched versus control	Unmatched elderly, n=39	p value[a] matched versus unmatched
ICU stay, days, mean ± SD	3.6±5.7	3.4±8.7	n.s.[b]	2.5±2.7	n.s.[b]
Total hospital stay, days, mean ± SD	20±12	22±17	n.s.[b]	18±11	n.s.[b]
Mortality, n %	10 (11)	2 (2)	0.017	3 (8)	n.s.
Postoperative morbidity, n %					
Overall	44 (47)	29 (31)	0.024	17 (44)	n.s.
≤4 segments resected	27/70 (39)	19/70 (27)	n.s.	14/34 (41)	n.s.
>4 segments resected	17/23 (74)	10/23 (44)	0.036	3/5 (60)	n.s.
Reinterventions, n %					
Overall	22 (24)	18 (19)	n.s.	8 (21)	n.s.
≤4 segments resected	10/70 (14)	11/70 (16)	n.s.	6/34 (18)	n.s.
>4 segments resected	12/23 (52)	7/23 (30)	n.s.	2/5 (40)	n.s.

[a] Pearson chi-square test
[b] Mann–Whitney U test
ASA, American Society of Anaesthesiologists

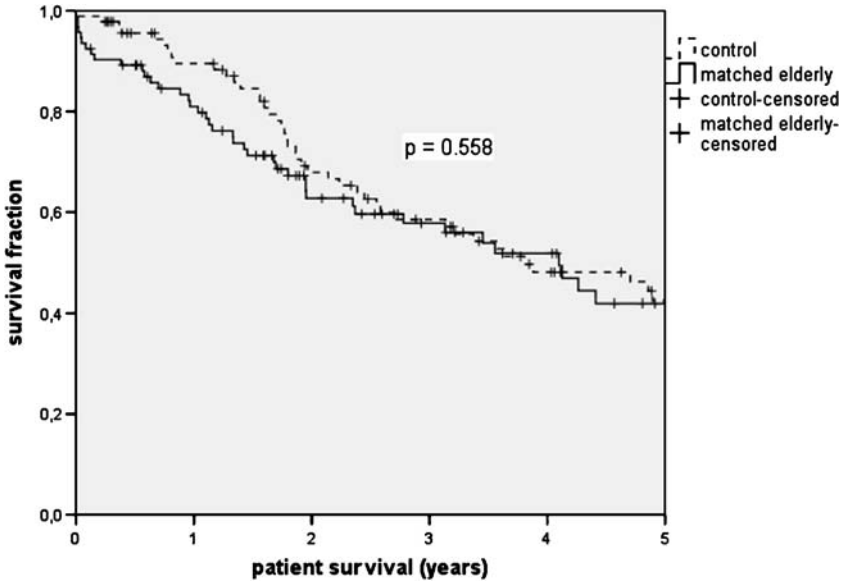

Figure 1 Patient survival.

One-, 3-, and 5-year disease-free survival in the matched patients was 63%, 45%, and 39%, respectively. One-, 3-, and 5-year disease-free survival in the control patients was 67%, 35%, and 31%, respectively p=0.468; Fig. 2.

Unified Model Analysis

Patient age, ASA grade, gender, and intraoperative blood transfusions showed no significant influence on patient survival. In univariate analysis, colorectal metastatic tumor or hepatocellular carcinoma, resection of five or more Couinaud segments, and irradical resection all significantly correlated with worse patient survival (Table 3).

Patient survival was further analyzed by entering patient age, ASA grade, type of disease, type of resection, and resection margin status as covariables in a multivariate analysis. In Cox regression analysis, resection margin status and ASA grade proved to be independent predictors of patient survival (Table 4).

Univariate analysis of disease-free survival in patients undergoing a radical resection for malignant disease showed that none of the study variables met the conditions to be entered in a multivariate analysis.

Discussion

Demographic studies have indicated a marked increase in life expectancy leading to 19% of the population aged 60 years or over at this moment in Europe and Northern

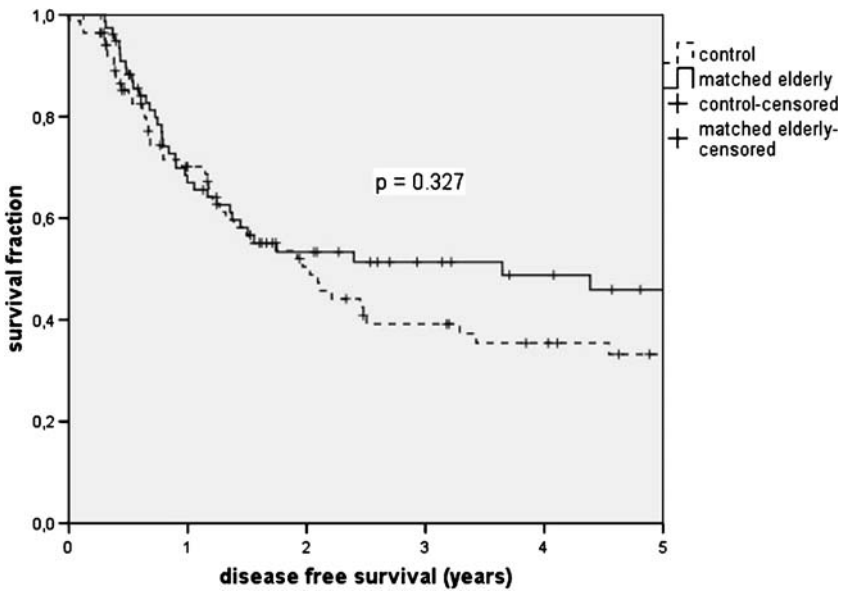

Figure 2 Disease-free survival.

Table 3 Univariate Analysis of Predictors of Patient Survival

	p value
Age <60/60+	0.558
Gender	0.484
ASA grade	0.054
Type of disease	0.041
Type of resection minor/major	0.022
Intraoperative blood transfusion <3/3+ RBCs	0.085
Resection margin status	0.002

America, Australia/New Zealand, and Japan. This figure is expected to increase to 33% in 2050 (http://www.un.org/esa/population/publications/aging99/fa99.htm). Epidemiologic surveys show over 50% of primary and secondary hepatic malignancies to occur in patients over 65 years (http://seer.cancer.gov), and liver surgery is the mainstay of curative treatment for these tumors.[17] It is therefore important to assess the influence of age on outcome after liver surgery. Previous studies addressing this issue have compared cohorts of elderly patients with younger patients treated in the same time period (Table 5).[6–11,18] However, comparing cohorts introduces a potential selection bias due to heterogeneity of patients and operative characteristics. In order to maximally reduce selection bias in this study, a matched control analysis was performed to ensure comparison of elderly and younger patients with the same diagnosis and the same extent of liver resection. Only non-cirrhotic patients undergoing a primary liver resection of three or more Couinaud segments were included.

A cutoff point at 70 years of age at the time of liver resection would allow for only 31 patients to be matched one-on-one to a control patient with the same type of liver resection for the same diagnosis. Including such a small number of patients would lead to an underpowered study. With a cutoff point for elderly and younger patients at 60 years of age at the time of liver resection, 93 of the patients over 60 years of age could be matched, which is over 70% of the patients over 60 years of age from this series. This was an important argument in an always arbitrary choice of a cutoff point for elderly and younger patients. The matched patients were not different from the unmatched patients with regard to age, gender, ASA grade, resection margin status, and intraoperative blood transfusions.

Hepatocellular carcinoma was more common in the matched patients, whereas non-colorectal, non-hepatocellular carcinoma was more common in the unmatched patients. This difference results from the fact that these non-colorectal, non-hepatocellular carcinoma have their peak incidence in patients over 60 years of age, so only for a minority of these patients a matching younger control patient could be found.

Mean age difference between the matched patients and the control patients was over 16 years, indicating a clinically relevant age difference. The mean difference in operation date was only 1.2 years, and for 95% of the matches, this difference was below 5 years, showing that no relevant historical bias was introduced.

Besides the obvious difference in age between the matched and the control patients, a significant difference regarding ASA grade was found. A higher proportion of matched patients were ASA grade 3 and a higher proportion of control patients were ASA grade 1. This was the only significant difference in baseline characteristics between the matched and the control patients. However, higher ASA grade could not be significantly correlated to a worse short-term outcome in terms of postoperative morbidity or in-hospital mortality, whereas age above 60 years was related to worse short-term outcome. Patients in ASA grade 3 are particularly represented among the subgroup of patients aged less then 60 years, since a patient over 60 years of age with ASA grade 3 will be more often deemed inoperable compared to a younger patient with ASA grade 3. This selection bias regarding ASA grade might explain the fact that a relation between ASA grade and short-term outcome could not be found in these series.

Short-term outcome was worse in matched patients compared to the control patients. Matched patients had a significantly higher in-hospital mortality rate (11%) compared to control patients (2%) in this study. In both of the control patients and in eight out of ten matched patients, the in-hospital mortality was due to liver insufficiency and sepsis.

The key to explaining the difference in in-hospital mortality might be a slower regeneration rate in patients over 60 years of age, making these patients more prone to liver insufficiency and sepsis. Liver regeneration occurs by inducing hyperplasia in the remnant liver volume. The initiation and synchronization of this regeneration response depends on the extent of liver resection. A substantially higher cellular replication rate is seen after major liver resection compared to minor liver resection.[19,20] An

Table 4 Multivariate Analysis of Predictors of Patient Survival

	p value	Hazard ratio 95% CI
Resection margin		
Radical		
Irrradical	0.002	2.44 (1.34–4.42)
ASA		
Grade 1		
Grade 2	0.084	1.61 (0.97–2.66)
Grades 3 or 4	0.016	2.21 (1.16–4.22)
Age		
<60 years		
≥60 years	0.213	1.01 (0.99–1.04)

Table 5 Literature Reports

	Group	Year	Country	Number of patients	3-year survival %		5-year survival %	
					<70 years	>70 years	<70 years	>70 years
CRM	Mazzoni et al.	2007	Italy	144 versus 53			38	30
	Nagano et al.	2005	Japan	150 versus 62			53	34
HCC	Ferrero et al.	2005	Italy	177 versus 64			32	49
	Hanazaki et al.	2001	Japan	283 versus 103			40	42
All indications	Menon et al.	2006	UK	390 versus 127	57	59		
	Cescon et al.	2003	Italy	99 versus 23	54	64		

CRM colorectal metastasis, *HCC* hepatocellular carcinoma

excellent summary of the molecular basis of this process has recently been described by Clavien et al.[21] Animal studies show the process of regeneration to be dependant of mediators similar to those found in acute inflammation. Mediators identified in the process of initiating the cell cycle are cytokines derived from Kupfer cells like tumor necrosis factor α and interleukin-6. After activation of the cell cycle, growth factors like epidermal growth factor, hepatocyte growth factor, transforming growth factor α and β, and other factors like platelet-derived serotonin and bile acids induce, maintain, and finally, terminate a full and synchronized regeneration phase. Lower expression of these mediators in patients over 60 years of age might impair the process of liver regeneration and thereby increase the risk of inadequate recovery of liver volume and lead to higher risks of clinical signs of liver failure after liver resection.

A previous study already showed a correlation between patient age and the risk of liver failure after primary liver resection.[22] Shimada et al. more recently showed a correlation between higher patient age and slower regeneration rate after right hemihepatectomy in humans.[23] In humans, no comparative studies regarding regeneration rate after hepatectomy in elderly versus younger patients have been performed, but Biondo-Simoes et al. recently showed a relevant delay in regeneration rate after major hepatectomy in elderly compared to younger rats.[24] Slower regeneration rates might well explain the higher in-hospital mortality, mostly due to liver insufficiency and sepsis, in patients over 60 years of age.

Despite significantly higher in-hospital mortality in the matched patients, 5-year patient survival was 42% in both groups, and 5-year disease-free survival was 39% in the matched and 31% in younger patients, respectively. These figures are concordant with recent studies showing 5-year patient survival rates of 30% to 49% in elderly patients compared to 32% to 53% in younger patients. This means that, despite the difference regarding short-term outcome, patients over 60 years of age show no difference in long-term outcome compared to younger patients. This suggests a relatively worse long-term prospect for younger patients surviving the hospitalization phase of a liver resection compared to patients over 60 years of age surviving this phase. While from previous literature it might already been known that long-term outcome is not different between elderly and younger patients, a new observation from this study is the paradox in survival patterns. Younger patients may show a far better in-hospital survival, but in the end, it still leads to the same prospects in terms of long-term survival compared to patients over 60 years of age. In return, the patient over 60 years of age has a higher risk of in-hospital mortality, but this is compensated by a relatively better prospect in terms of long-term survival, which might be due to less aggressive tumor biology in these patients. However, survival analysis showed no difference in patient survival or disease-free survival between younger patients surviving the hospitalization phase of a liver resection compared to patients over 60 years of age surviving the hospitalization phase of a liver resection in our population (data not shown).

Multivariate analysis shows the resection margin status and ASA grade to be independent predictors of long-term patient survival. As indicated in Table 4, ASA grades 3 or 4 patients have an increased chance of long-term mortality compared to ASA grade 1 patients with a hazard ratio of 2.21. Age itself was not an independent predictor of long-term survival.

This finding underlines the obvious statement to strive for tumor-free margins, but it also urges those involved in preoperative patient selection for major liver resections rather to consider the ASA grade than patient age as a predictive factor for long-term survival.

Conclusion

The influence of advanced age on the outcome after liver resection has never been explored in a matched control study. The current study paradoxically shows a worse short-term outcome in patients over 60 years of age in terms of in-

hospital mortality and morbidity, while their overall long-term survival is not different from control patients. This observation confirms the clinical observation that patients over 60 years of age have higher risks after liver resections, while at the same time, this does not result in a difference in long-term outcome. Multivariate analysis shows tumor-free resection margins and lower ASA grade to be independent predictors of long-term patient survival, while age itself was not associated with long-term patient survival.

Acknowledgment No financial support received.

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J Gastrointest Surg (2008) 12:2204–2211
DOI 10.1007/s11605-008-0586-8

Safety of Conservative Management of Bile Leakage after Hepatectomy with Biliary Reconstruction

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Received: 31 March 2008 / Accepted: 16 June 2008 / Published online: 19 July 2008

Abstract
Background The risks associated with the conservative management of bile leakage after hepatectomy and associated cholangiojejunostomy are not well defined.
Aim The aim of this study was to evaluate incidence and severity of complications associated with bile leakages after liver resection with biliary reconstruction.
Patients and methods Clinical data from 1,034 consecutive patients who underwent liver resection were prospectively collected and reviewed. Bile leakage occurred in 25 out of 119 patients (21.0%) who underwent hepatectomy with biliary reconstruction (group 1) and in 42 out of 915 patients (4.6%) without biliary anastomosis (group 2; $p<0.001$). Serum albumin and bilirubin levels were the only preoperative factors significantly different between the two groups. Lymphadenectomy was more frequently performed in patients of group 1 (88% vs 16.7, $p<0.001$).
Results Mortality rates were similar in the two groups (8% in group 1 vs 2.3% in group 2, $p=0.28$). One or more postoperative complications occurred in 68% in group 1 and in 40.4% in group 2 ($p=0.02$). The incidence of sepsis (32% vs 7.1%, $p=0.01$), intra-abdominal abscess (12% vs 0, p=0.04), and abdominal bleeding (28% vs 0, $p=0.006$) was significantly higher in group 1. Bile leaks spontaneously healed in 52% of patients in group 1 vs 76.2% in group 2 ($p=0.04$). In order to identify independent predictive factors for abdominal bleeding, we compared clinical data of patients with abdominal bleeding (seven patients) and without abdominal bleeding (18 patients) after hepatectomy and biliary reconstruction. Stepwise logistic regression analysis identified the number of reconstructed bile ducts as an independent predictive factor of abdominal bleeding ($p=0.038$).
Conclusions Conservative management of bile leakage after liver resection with biliary reconstruction is associated with higher rates of morbidity. The most severe complication is abdominal bleeding, which is related to the number of bile ducts requiring reconstruction.

Keywords Bile leakage · Hepatectomy · Cholangiojejunostomy · Abdominal bleeding

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Introduction

Bile leakage is considered the Achilles' heel of liver surgery and it is related to an increased rate of sepsis, liver failure, and postoperative mortality.[1] Despite the decrease of overall postoperative complications after hepatectomy, the incidence of bile leakage has not changed in the last decades, ranging from 2.6% to 12% in recent large series.[1–3] Bile leakage after hepatectomy without biliary reconstruction is usually managed by conservative treatment. Expectant management is successful in most cases.[1,4–7] Some authors analyzed the outcome

of bile leakage after hepaticojejunostomy, mainly as a part of different procedures (pancreatoduodenectomy, proximal bile duct resection, and bile digestive bypass for malignant and benign disease).[8–13] Only few reports focus on the management of bile leakage after hepatic resection with biliary reconstruction.[14]

We hypothesized that bile leakage following hepatic resection and concomitant cholangiojejunostomy had a different evolution could be associated to a higher number of severe complications and therefore benefit from a more aggressive management strategy.

The aim of this study was to compare the incidence and the clinical outcome of bile leakage after hepatic resection with and without biliary anastomosis.

Patients and Methods

Prospectively collected clinical data of 1,034 consecutive patients who underwent liver resection in our department between January 1989 and December 2006 were retrospectively reviewed. These 1,034 patients were divided into two groups: 119 (11.5%) with biliary reconstruction and 915 (88.5%) without biliary reconstruction.

Preoperative Management

Preoperative workup consisted of blood examinations, abdominal ultrasound, and angio-computed-tomography (CT) scan. In selected cases, a magnetic resonance was performed. Preoperative imaging of the biliary tree was performed only in presence of cholestasis. Since 1998, every patient scheduled for a major hepatectomy underwent CT–volumetry of future remnant liver (FRL). Preoperative portal vein embolization was planned when the estimated FRL was ≤25% in patients with a normal liver or ≤30% in those with chronic liver disease. Since 2000, indocyanine green (ICG) retention test was routinely performed to evaluate liver function in patients with serum bilirubin level of <2 mg/dl. The resection volume was determined based on ICG retention rate at 15 min; patients with ICG retention test higher than 10% were excluded from the scheduled major hepatectomy. Indications for preoperative biliary drainage (PBD) in jaundiced patients were: scheduled preoperative portal vein embolization, signs of cholangitis, and malnutrition (serum albumin lower than 3 g/dl). In our center, patients underwent PBD by percutaneous transhepatic biliary drainage (PTBD) of the remnant liver, with internal–external drainage whenever possible. Some patients who were referred to our center had already undergone transhepatic or endoscopic biliary drainage elsewhere.

Surgical Management

Intraoperative ultrasonography (Aloka SSD1200 with 7.5-MHz intraoperative linear probe) was routinely performed as the first step in order to assess the site and the extension of the disease and the relationship of the tumor with major intrahepatic vessels. Continuous or intermittent pedicle clamping was usually performed during parenchymal transection. During the last years, the use of pedicle clamping decreased and most resections were performed without Pringle maneuver, in accord with the results of our recent randomized clinical study.[15] During major liver resections, bile duct interruption was usually performed at the end of the hepatectomy. When bile duct resection was associated with major hepatectomy, bilioenteric continuity was reestablished by Roux-en Y cholangiojejunostomy. The anastomosis was performed by anastomosing the bile duct wall and the seromuscular layer of the intestine with 5–0 or 6–0 interrupted absorbable monofilament. When multiple intrahepatic bile ducts were present, they were grouped to form one or two anastomotic orifices. A transanastomotic biliary drainage, either transhepatic or transjejunal, was utilized according to surgeon preference. An intraoperative cholangiography or a bile leakage test, injecting isotonic solution through the cystic stump and clamping the distal common bile duct, was selectively performed in patients with a suspected bile duct lesion. When necessary, biliostasis was obtained by suturing the identified bile leak site using 5–0 or 6–0 absorbable monofilament. An abdominal drain was usually employed and it was removed when the drainage was serous and not bile-stained, usually not before the fourth postoperative day.

Definition

Major hepatectomy is defined as resection of three or more Couinaud's segments. Extended hepatectomy is defined as resection of five or more Couinaud's segments. Types of hepatectomy were classified according to Brisbane 2000 Terminology.[16] Bile leakage was defined as the drainage of 50 ml or more of bile from the surgical drain or from a drainage of an abdominal collection, lasting 3 days or more.[7]

Liver dysfunction was defined as both PT<50% and serum bilirubin level of >5 mg/100 mL for three or more consecutive days.[3–4]

Operative mortality was defined as death within 60 days after operation or occurring before discharge from hospital.

Management of Postoperative Bile Leakage

Conservative management was the initial treatment of postoperative bile leakage in all patients. Every patient

underwent abdominal ultrasonography and/or CT scan in order to identify associated collections and antibiotic therapy was administrated according to clinical data. Conservative management failure was defined as the necessity of interventional procedures because of associated complications or because of persisting high drainage output after 30 days. Immediate reoperation was considered only in case of biliary peritonitis.

Statistical Analysis

Continuous variables were reported as mean (±SD), unless otherwise stated, and compared by Student *t* test. Categorical variables were compared by χ-square test or Fisher exact test, as appropriate. A *p* value less than 0.05 was considered significant for all the tests. Multivariate analysis was performed by including all the variables significant ($p<0.05$) or borderline significant ($p<0.1$) at univariate analysis into a stepwise regression model.

Results

Bile leakage occurred in 25 out of 119 patients (21.0%) who underwent hepatectomy with biliary reconstruction (group 1) and in 42 out of 915 patients (4.6%) without biliary anastomosis (group 2; $p<0.001$). In group 1, intraoperative transanastomotic stent was inserted in ten patients out of 25 with postoperative bile leakage (40%) and in 26 patients out of 94 patients who did not present postoperative bile leakage (27.6%, $p=0.232$).

Preoperative and operative characteristics of both groups are summarized in Table 1. Serum albumin and bilirubin levels were the only preoperative factors significantly different between the two groups. Lymphadenectomy was more frequently performed in patients with hepatectomy and biliary reconstruction (88% vs 16.7, $p<0.001$).

Outcome

Postoperative outcome of the patients with bile leakage is reported in Table 2.

The mortality rates were similar in the two groups. Two patients died in group 1: one because of sepsis and liver failure on postoperative day 74 and one of abdominal bleeding on postoperative day 3. One patient of group 2 died because of sepsis and liver failure on postoperative day 53.

One or more postoperative complications associated with bile leakage occurred in 68% (17 of 25) in group 1 and in 40.4% (17 of 42) in group 2 ($p=0.029$). In particular, the incidence of sepsis (8 [32%] vs 3 [7.1%], $p=0.011$), intra-abdominal abscess (3 [12%] vs 0, $p=0.048$), and abdominal bleeding (7 [28%] vs 0, $p=0.006$) was significantly higher in the group with biliary anastomoses. Perioperative blood transfusion rate was significantly higher in patients of

Table 1 Preoperative and Operative Characteristics of Patients with Bile Leakage

	Incidence of biliary leak with or without hepaticojejunostomy (HJ)		*p* value
	With HJ ($n=25$)	Without HJ ($n=42$)	
Preoperative			
Age	64.9 (41–80)	61.6 (58–78)	0.188
Sex	17/8	22/20	0.210
Total bilirubin (mg/dl)	5.1±4.8	0.8±0.5	<0.001
Albumin (g/dl)	3.4±0.6	3.8±0.5	0.010
Prothrombin time (%)	98.2±10.8	94.9±13.6	0.331
Platelet count	213.000±131	220.000±917	0.816
ICGR15[a]	14.7±29.0	6.0±6.18	0.146
Operative			
Major hepatectomy	19 (76%)	25 (59.5%)	0.194
Right hepatectomy ± Sg1	2 (8%)	5 (11.9%)	0.475
Left hepatectomy ± Sg1	7 (28%)	4 (9.5%)	0.053
Right trisectionectomy	6 (24%)	9 (21.4%)	0.517
Left trisectionectomy	2 (8%)	5 (11.9%)	0.475
Resected segments	4.0±1.5	3.3±1.5	0.078
Lymphadenectomy[b]	22 (88%)	7 (16.7%)	<0.001
Vascular resection	5 (20%)	2 (4.7%)	0.092
Pedicle clamping	8 (32%)	21 (50%)	0.150

[a] Indocyanine green retention test at 15 min; data are available from 36 patients (ten with biliary reconstruction, 26 without biliary reconstruction) since 2000

[b] Lymphadenectomy was extended to liver pedicle, common hepatic artery, and retropancreatic nodes

Table 2 Outcome of Patients with Bile Leakage

	Incidence of biliary leak with or without hepaticojejunostomy (HJ)		*p* value
	With HJ (*n*=25)	Without HJ (*n*=42)	
Mortality	2 (8%)	1 (2.3%)	0.282
Morbidity	17 (68%)	17 (40.4%)	0.029
Infectious morbidity	11 (44%)	7 (16.6%)	0.014
Intra-abdominal abscess	3 (12%)	0	0.048
Lung infection	4 (16%)	4 (9.5%)	0.337
Sepsis	8 (32%)	3 (7.1%)	0.011
Noninfectious morbidity	12 (48%)	7 (16.6%)	0.007
Abdominal bleeding	7 (28%)	0	0.006
Liver failure	4 (16%)	4 (8.9)	0.337
Blood transfusion rate	17 (68%)	8 (19%)	0.001
Reoperation rate	8 (32%)	3 (6.6%)	0.011
Hospital stay (days, median)	53.2 (13–127)	21.8 (13–127)	<0.001

group 1 (17 [68%] vs 8 [19%], p=0.001). The rate of reintervention was higher in group 1 (8 [32%] vs 3 [7.14%], p=0.011). The length of hospital stay was significantly shorter for patients of group 2 (53.2±26.9 vs 21.8± 14.19 days, p<0.001).

Management of Biliary Leakage

Clinical data regarding bile leakage are reported in Table 3. Mean length of bile leakage was 63.4±44.7 days in group 1 and 34.1±36.60 days in group 2 (p=0.014). Mean daily bile drain output at day 5 from the onset of leak was 257.8 ±265.3 cm^3 in group 1 vs 136.3±174.7 cm^3 in group 2 (p= 0.045) and at day 10 183.8±174.6 vs 94.6±109.8 cm^3 (p= 0.045).

In group 1, conservative management was successful with spontaneous healing in 13 patients (52%) with a median healing time of 63.4 (10–154) days. One of these patients underwent three laparotomies because of relapsing abdominal bleeding, without attempting any bile leakage treatment. In 12 patients (48%), conservative management failed. Six patients underwent percutaneous interventional procedure after a median waiting time of 31 days after the diagnosis of bile leakage. Healing was obtained in five patients after a median time of 86.5 days (range 26–150) after the procedure. One patient with persisting bile leakage underwent laparotomy on postoperative day 35; he died of liver failure 74 days after intervention with persisting bile leakage. The remaining six patients required emergency reintervention for abdominal bleeding and in five of them the biliary enteric anastomosis was reconstructed. Surgical reconstruction was never completely successful: in three patients, a low-output fistula persisted after reoperation and spontaneously healed after a median of 54.7 days (range 26–86); one patient required multiple transhepatic biliary drainages and the bile leakage healed 86 days after intervention; one patient died of progressive tumor disease after 6 months with a persisting fistula. One patient died of abdominal bleeding.

In group 2, conservative management was successful with spontaneous healing in 32 patients (76.2% vs 52%, p= 0.041) with a median healing time of 34.1 (range 4–

Table 3 Bile Leakage Characteristics

	Incidence of biliary leak with or without hepaticojejunostomy (HJ)		*p* value
	With HJ (*n*=25)	Without HJ (*n*=42)	
Postoperative day of onset	8.3±26.9	8.1±8.1	0.908
Median length (days)	63.4±44.7	34.1±36.6	0.014
Drainage output (mL)			
Day 1[a]	412.9±514.9	278.9±290.3	0.209
Day 3[a]	279.5±264.6	235.4±335.4	0.613
Day 5[a]	257.8±265.3	136.3±174.7	0.045
Day 10[a]	183.8±174.6	94.6±109.8	0.045
Spontaneous healing	13 (52%)	32 (76.2%)	0.041
Healing time (days)	63.4 (10–154)	34.1 (4–180)	0.014

[a] Days are computed from bile leakage onset

180) days. In 10 patients (23.8%), conservative management failed. One patient underwent laparotomy because of biliary peritonitis: the site of bile leakage on the liver cut surface was sutured and complete postoperative healing was obtained. Nine patients underwent endoscopic retrograde cholangiopancreatography (ERCP) because of persisting high output and leakage healing was obtained in six cases. In these patients, the mean delay from bile leakage diagnosis was 36.5 days (range 10–90). One patient with persistent bile leakage underwent laparotomy, but he died of tumor progression 6 months later with continued bile leakage. The remaining two patients presented with severe sepsis and both underwent further ERCP and PTBD; one patient died because of sepsis with persisting bile leakage 46 days after its onset and the other died of tumor progression 5 months later with persisting bile leakage from abdominal drainage.

The site of bile leakage in patients with spontaneous healing of group 1 could not be identified in patients where a transanastomotic stent had not been inserted (seven out of 13 patients). Only four out of the remaining six patients with intraoperative transanastomotic stent underwent postoperative cholangiography: the site of bile leakage was the cholangiojejunostomy in three patients and liver cut surface in one patient. Six out of 12 patients with persistent bile leak underwent emergency reintervention for abdominal bleeding and in all of them the site of bile leak was the cholangiojejunostomy. The six remaining patients with persistent bile leak underwent PTBD and in all of them the site of bile leakage was the cholangiojejunostomy.

Abdominal Bleeding

Anastomotic leak of the cholangiojejunostomy was in close association with abdominal bleeding. The postoperative course of seven patients was complicated by abdominal bleeding and all of them underwent a laparotomy on emergency. Site of bleeding was always arterial. In particular, in three patients, common hepatic artery was identified as the site of bleeding; in two patients, the site was right hepatic artery, in one left hepatic artery. One patient died intraoperatively and the site of bleeding was not identified. Three patients underwent relaparotomy because of further bleeding. One patient suffered from three episodes of abdominal bleeding. Mortality was the same in patients with and without abdominal bleeding (1/7 patients [14.2%] vs 1/18 patients [5.5%], $p=0.496$).

Multivariate analysis In order to identify independent predictive factors for abdominal bleeding, we compared clinical data of patients with and without abdominal bleeding after hepatectomy and biliary reconstruction (Table 4). The number of bile ducts requiring reconstruction, left hepatectomy with or without segment 1, arterial hypertension, intraoperative blood loss of >300 cm^3, and postoperative day of bile leakage onset of >10 days were considered for multivariate analysis (Table 5). Stepwise logistic regression analysis identified the number of reconstructed ducts as the only independent predictive factor for abdominal bleeding ($p=0.038$).

Discussion

Conservative management is reported by many authors as the treatment of choice in patients with postoperative bile leakage.[1,5–7] Spontaneous healing of bile leakage after hepatectomy without bile duct resection usually happens with expectant management, with low rates of associated morbidity.[17–20] Even in the present series of 915 hepatectomies without biliary reconstruction, the rate of successful conservative treatment is high (76.2%) and few patients required reintervention. Some authors advocate the same conservative strategy even for the treatment of bile leakage occurred after hepatectomy with bile duct resection.[9,14] Nevertheless, few data are reported concerning biliary complications after hepatic resection with biliary reconstruction.[14]

Previous studies analyzed bile leakage following biliary anastomosis as a complication of several procedures (pancreatoduodenectomy, hepaticojejunostomy for either malignant or benign disease).[8–13] Antolovic et al.[9] reported results of 519 patients who underwent hepaticojejunostomy. The incidence of bile leakage was 5.6% but varied considerably depending on the type of procedure. Only ten patients underwent hepatic resection with biliary reconstruction and five of them (50%) developed postoperative bile leakage. Therefore, the authors reported at univariate and multivariate analysis that simultaneous liver resection was a risk factor for bile leakage and for surgical morbidity.

Nagino et al.[14] recently reported a series of 423 patients who underwent intra-hepaticocholangiojejunostomy following hepatectomy. The authors suggested that bile leakage can be managed nonoperatively even after liver resection with biliary reconstruction. Nevertheless, the incidence of bile leakage is 3.6% in the last 5 years, which is lower than those reported in other series (6.2–22.5% in series of hilar cholangiocarcinoma).[21–28] Moreover, most reconstructed bile ducts were preoperatively drained by percutaneous biliary drains (median of two per patient) and all reconstructed bile ducts were drained by transjejunal route. Whether or not routine intraductal drainage which is not routinely performed by all hepatic surgeons is responsible for these results remains controversial.

Table 4 Clinical Characteristics and Outcomes of Patients with Bile Leakage After Hepatectomy with Biliary Reconstruction

	Abdominal bleeding		*p* value
	Yes (*n*=7)	No (*n*=18)	
Age	70.1 (57–78)	62.9 (49–80)	0.130
Sex	4 (57.1%)	13 (72.2%)	0.393
Arterial hypertension	5 (71.4%)	5 (27.8%)	0.045
Preoperative total bilirubin (mg/dl)	6.0±5.6	4.8±4.6	0.525
Preoperative albumin (g/dl)	3.4±0.8	3.4±0.6	0.843
Hilar cholangiocarcinoma	5 (71.4%)	10 (55.5%)	0.467
Gallbladder cancer	2 (28.5%)	5 (27.8%)	1
Intrahepatic cholangiocarcinoma	0	1 (5.5%)	1
Colorectal metastasis	0	2 (11,1%)	1
Major hepatectomy	5 (71.4%)	14 (77.7%)	1
Right hepatectomy ± Sg1	0	2 (11.1%)	1
Left hepatectomy ± Sg1	4 (57.1%)	3 (16.6%)	0.043
Right trisectionectomy	1 (14.2%)	5 (27.7%)	0.443
Left trisectionectomy	0	2 (11.1%)	1
Number of segments	3.8±1.6	4.0±1.4	0.834
Vascular resection	1 (14.2%)	4 (22.2%)	1
Pedicle clamping	1 (14.2%)	7 (38.8%)	0.362
Transanastomotic stent	3 (42.8%)	6 (33.3%)	0.656
Mean reconstructed biliary ducts	2.4±0.8	1.7±0.7	0.025
Operative blood loss (mL)	365±188.1	200.9±154.3	0.107
Operative blood loss >300 mL	3 (42.8%)	3 (16.6%)	0.193
Postoperative day of onset	3.8±3.7	9.7±6.2	0.060
Postoperative day of onset >10	0	7 (38.8%)	0.066
Drainage output (mL)			
Day 1[a]	690.0±927.7	326.3±300.7	0.173
Day 3[a]	338.0±332.1	260.0±248.7	0.582
Day 5[a]	403.0±416.8	209.3±189.3	0.162
Day 10[a]	210.0±176.6	175.0±179.3	0.708

In fact, our results showed that the expectant treatment for bile leakage after cholangiojejunostomy and hepatic resection is not always safe and spontaneous healing happens significantly less frequently than after hepatectomy without bile duct resection.

In patients who presented with bile leakage following biliary reconstruction, higher rates of infectious morbidity and abdominal bleeding were observed. Despite the fact that the mortality rates in the two groups were similar, abdominal bleeding should be considered a serious complication that has high association with biliary anastomotic leak. Several studies suggested that perioperative blood loss and transfusions are negative prognostic factors on postoperative outcome, tumor recurrence, and long-term survival.[29–32]

Table 5 Risk Factors for Abdominal Bleeding in Patients with Bile Leakage After Hepatectomy with Biliary Reconstruction

	Multivariate analysis			
	OR	95% CI		*p* value
		Lower	Upper	
Operative blood loss >300 mL	4.000	0.265	60.325	0.317
Postoperative day of onset >10	0.849	0.603	1.197	0.351
Arterial hypertension	10.823	0.958	122.215	0.054
Number of reconstructed ducts	5.701	1.101	29.522	0.038
Left hepatectomy ± Sg1	5.116	0.375	69.806	0.221

Multivariate analysis identified the number of reconstructed ducts as the only independent predictive factor of abdominal bleeding. The etiology of abdominal bleeding is uncertain. It has been suggested that vascular lesions responsible for delayed hemorrhage result from a combination of bile leakage and local sepsis that may cause erosion of blood vessels often weakened by skeletonization after extensive lymphadenectomy. Lymph node dissection of the hepatic hilus, around the pancreatic head and along the common hepatic artery, is usually indicated in patients with biliary tumors (peripheral or hilar cholangiocarcinoma, gallbladder cancer).[33,34] De Castro et al.[10] stated that anastomosis on the segmental bile ducts were independent predictors of bile leakage, but no data are reported on the associated morbidity. Therefore, the use of intraluminal transanastomotic biliary drainage catheters (single or multiple) when the biliary anastomosis is performed on segmental bile ducts is recommended, especially if ducts are unusually small. In addition, in the present series, a lymphadenectomy was more frequently performed in patients with hepatectomy with biliary reconstruction. Hence, we propose to protect the skeletonized vessels with omental flaps or topical agents after extensive lymphadenectomy.

In our series, no patient with bile leakage that suffered from abdominal bleeding had been treated prior to the hemorrhage with percutaneous biliary drainage. In this group of patients, conservative management was not adequate and a more expedited use of PTBD may have reduced the risk of bleeding. In the univariate analysis of this study, the presence of transanastomotic stent was not a protective factor for the risk of abdominal bleeding. Nevertheless, persistent bile leakage in five out of six patients who underwent PTBD healed promptly after this procedure. Accordingly, PTBD promotes bile leakage healing and therefore decreases the risk of abdominal bleeding. In these patients, it is crucial to reduce the waiting time before percutaneous biliary drainage, eventually draining all the reconstructed ducts.

Patients with bile leakage following hepatic resection without biliary reconstruction can be discharged when the trend of bile output is decreasing and followed in the outpatient clinic. On the other hand, patients with bile leakage with biliary reconstruction should not be discharged before complete biliary healing.

In conclusion, conservative management of bile leakage is less successful and less safe after hepatectomy with cholangiojejunostomy than after hepatectomy without bile duct reconstruction. Operative management also achieves little success. Early invasive treatment should be considered in order to decrease the risk of infectious complications and abdominal bleeding.

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J Gastrointest Surg (2008) 12:2212–2220
DOI 10.1007/s11605-008-0597-5

Surgical Treatment Concepts for Acute Lower Gastrointestinal Bleeding

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Received: 23 May 2008 / Accepted: 25 June 2008 / Published online: 18 July 2008

Abstract
Background and purpose To this day, the diagnostic and therapeutic strategy for acute lower gastrointestinal hemorrhage requiring transfusion varies among different hospitals. The purpose of this paper was to evaluate our own data on the group of patients presented and to outline our diagnostic and therapeutic regime taking into account the literature of the past 30 years.
Methods Following prospective data collection on 63 patients of a university hospital (40 male, 23 female patients) who received surgical intervention for acute lower intestinal hemorrhage requiring transfusion, we retrospectively analyzed the data. After a medical history had been taken, all patients underwent clinical examination, including digital palpation; 62 patients underwent procto-rectoscopy, 38 gastroscopy and colonoscopy, 52 patients colonoscopy only, and 45 patients gastroscopy only. Angiography was applied in 14 cases and scintigraphy in 20 cases.
Results Diagnostic procedures to localize hemorrhage were successful in 61 cases, 41 of which through endoscopy, 12 through angiography, and eight through scintigraphy. Of our group of patients, 32 suffered from a bleeding colonic diverticulum, eight from angiodysplasia, and five from bleeding small bowel diverticula. Five patients had inflammatory bowel disease and three neoplasia. Among the surgical interventions, segmental resections were performed most frequently (15 sigmoidectomies, 11 small bowel segmental resections, 11 left hemicolectomies, seven right hemicolectomies, one proctectomy). Subtotal colectomies were carried out in ten cases. The complication rate for this group of critically ill, negatively selected patients was 60.3% and the mortality rate was 15.9%.
Conclusions Examination and stabilization of the patient is directly followed by diagnostic localization. Today, we primarily rely on nonsurgical control of hemorrhage by endoscopy or angiography; the indication for surgery is mainly limited to peracute, uncontrollable, and recurrent forms. In the case of surgery, intestinal segmental resection is recommended after identification of the lesion; if the localization of colonic hemorrhage is uncertain, subtotal resection is the method of choice. For stable patients with unverifiable small-bowel hemorrhage we recommend regular re-evaluation.

Keywords Lower gastrointestinal bleeding · Therapeutic strategies · Endoscopy · Angiography · Surgery

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Introduction

If an intestinal bleeding originates in the area between the duodenojejunal flexure (ligament of Treitz) and the anocutaneous line, it is defined as lower gastrointestinal bleeding (20% of all gastrointestinal (GI) bleedings). Hemorrhage of oral genesis above the ligament of Treitz is called bleeding of the upper gastrointestinal tract (80% of all GI bleeding), which include rare bleeding into the biliary tract (hemobilia) and the pancreatic duct system (hemosuccus pancreaticus). The frequencies of causes for hemorrhage vary with age. Young patients are more often hospitalized with bleeding

Meckel's diverticulum (bleeding from ectopic ulcerating gastric mucosa), whereas in the later decades of life colonic diverticula and neoplasms are more prevalent (Table 1).

Apart from the anatomic localization of their origin and their pathophysiologic genesis, hemorrhage can be subdivided into chronic and acute hemorrhage based on the chronology of their occurrence. Clinically, chronic bleeding often remains occult and is discovered coincidentally through early detection tests (hemoccult test) or other routine blood counts (anemia), while acute bleeding usually manifests in the excretion of blood in the form of hematochezia or melena. Hematochezia is the macroscopically clearly visible passage of blood per rectum which can either be seen on top of the stools or on the toilet paper or may already be mixed with the stools. It is often a singular symptom in otherwise well patients.[10] Melena, in contrast, is defined as the passage of black stool resulting from oxygenation of hematin.[11] Elevated blood loss within a short time and failure of the organism to adapt makes acute bleeding often more fulminant and life-threatening than chronic bleeding. The identification of the source of bleeding still remains a challenging task today even where acute bleeding is concerned, in spite of the frequently intense passage of blood per rectum. Although acute lower GI bleeding stops in 80% of the cases, 25% of the patients suffer from recurrent bleeding.[3] This paper primarily addresses the clinical picture of acute lower gastrointestinal hemorrhage, for which the technical literature indicates an overall mortality of 2% to 4%.[1,2] To illustrate the special risk of that group of patients whose hemorrhage cannot be managed either endoscopically or radiologically, as a surgical clinic we analyzed the results of selected patients with an indication for surgery.

Material and Methods

Following prospective data collection on 63 patients with a lower GI bleeding diagnosis admitted to the Surgical Clinic of Schleswig–Holstein University Hospital, Lübeck Campus, between June 1999 and January 2008, we retrospectively analyzed and evaluated their medical records. Among the patients were 40 men (63.5%) with an average age of 69.3± 10.7 years (ranging from 41 to 89 years) and 23 women (36.5%) with an average age of 71.6±14.8 years (ranging from 39 to 97 years). The total average age was 70.1± 12.3 years (ranging from 39 to 97 years).

Table 1 Major Etiologic Factors of Lower Gastrointestinal Hemorrhage as a Function of Age Taking into Account the Literature of the Past Three Decades

Age group	Etiology
Childhood and adolescence	Meckel's diverticulum, intestinal duplication, volvulus
Adulthood	Inflammatory bowel disease (IBD), adenoma, colonic diverticulum
Senium	Colonic diverticulum, angiodysplasia, neoplasia

The analysis covers all patients with a primary acute bleeding of the lower gastrointestinal tract requiring transfusion. Another obligatory criterion for inclusion in this analysis is a surgical intervention performed during the hospital stay. The group with primary hemorrhage includes those patients who were admitted to our clinic for inpatient treatment of blood loss per rectum (leading admission diagnosis).

Patients with secondary hemorrhage that occurred while already admitted (hospitalized patients) are excluded; the same applies to patients referred to our clinic from another hospital. Further exclusion criteria are traumatic bleeding and bleeding that occurred after iatrogenic invasive intervention in the gastrointestinal tract, including surgery or therapeutic colonoscopy. Occult bleeding from the lower gastrointestinal tract detected, for example, due to chronic anemia of unknown origin has not been included either, even if blood transfusion was required.

In addition to these primary exclusion criteria, we secondarily excluded all patients whose medical records were incomplete (at least one target parameter missing).

As to methodology, we carried out the standardized diagnostic and therapeutic steps as illustrated in Fig. 1 to identify the source of bleeding if the symptom of hematochezia or melena occurred.

The prospective documentation consisted of a complete data collection. We compared our own data with those of the English and German literature of the past 30 years available in medical databases.

Results

Between 1999 and 2008, 63 patients were treated for acute bleeding from the lower gastrointestinal tract. Among them were 37 patients (58.7%) with bleeding diverticula, of these 32 with a colonic diverticulum (50.8%) and five with a small intestinal diverticulum (7.9%), eight patients (12.7%) with angiodysplasia, five patients (7.9%) with chronic inflammatory bowel disease, three patients (4.8%) with neoplasms, and ten patients (16.1%) with other diagnoses (fistulas, simple rectal ulcers, hemorrhoids, etc.).

In the age group under 65 years (n=22) the causal diagnoses were distributed as follows: seven patients (31.8%) with bleeding diverticula, two patients (9.1%) with neoplasms, three patients (13.6%) with chronic inflammatory bowel disease, five patients (22.7%) with angiodysplasia, and five patients (22.7%) with other diagnoses.

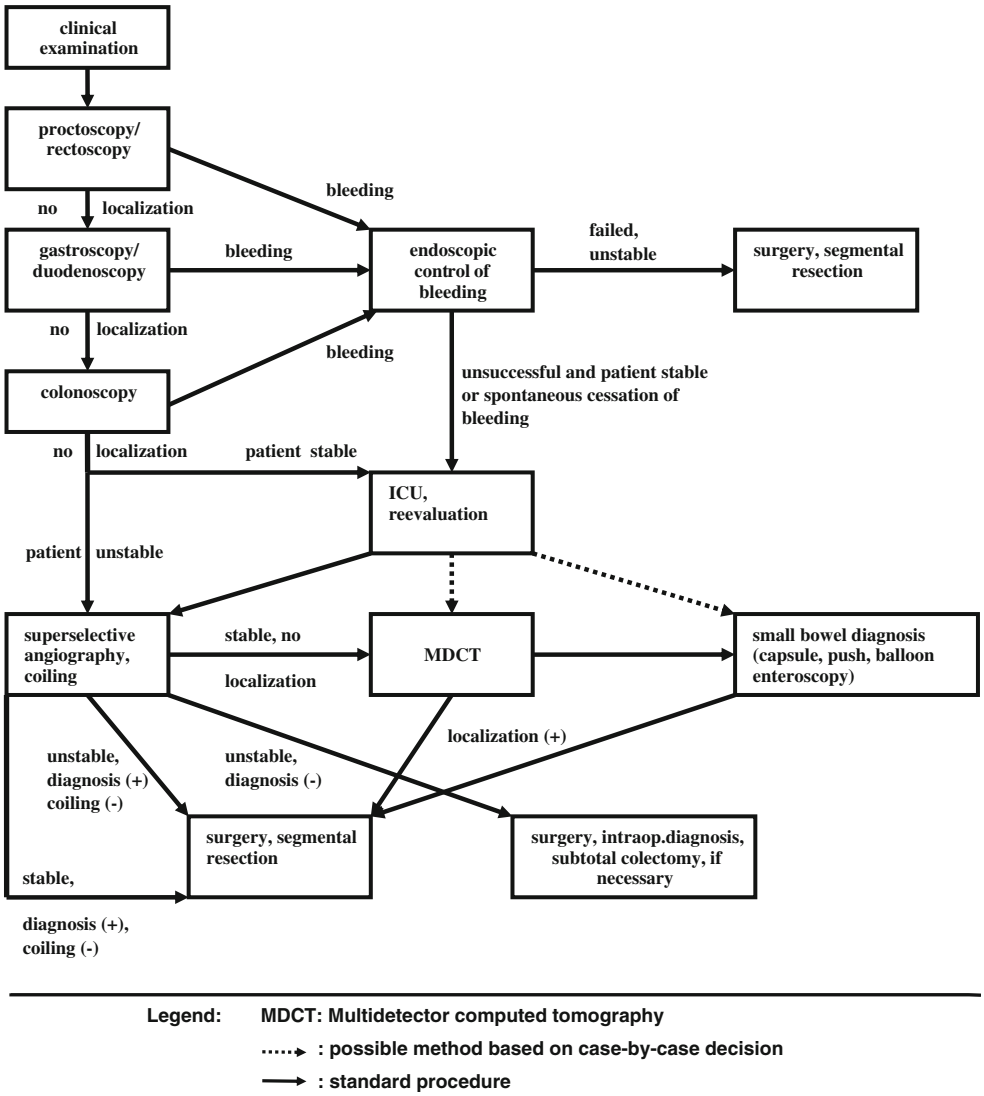

Figure 1 Diagnostic and therapeutic path followed by our hospital in cases of hematochezia or melena with hemodynamic effects.

In the age group above 65 years (n=41), the distribution was as follows: 30 patients (73.2%) with bleeding diverticula, one patient (2.4%) with neoplasia, two patients (4.9%) with chronic inflammatory bowel disease, three patients (7.3%) with angiodysplasia, and five patients (12.2%) with other diagnoses (Table 2).

All 63 patients were subjected to an initial physical examination, with a proctoscopy and rectoscopy performed on 62 patients (98.4%) immediately after admission. Subsequent diagnostic procedures included endoscopy performed on 59 patients (93.7%), gastroscopy on 45 patients, and colonoscopy on 52 patients. Thirty-eight

Table 2 Genesis of Hemorrhage in Acute Lower Gastrointestinal Bleeding (n=63 patients)—Absolute (Total) Numbers and as a Function of Age (<65 years; >65 years)

Etiology	<65 years		>65 years		Total	
	n	(%)	n	(%)	n	(%)
Colonic diverticulum	5	22.7	27	65.9	32	50.8
Angiodysplasia	5	22.7	3	7.3	8	12.7
Small bowel diverticulum	2	9.1	3	7.3	5	7.9
IBD	3	13.6	2	4.9	5	7.9
Neoplasia	2	9.1	1	2.4	3	4.8
Other	5	22.7	5	12.2	10	16.1

patients (60.3%) required both gastroscopy and colonoscopy. In four cases (6.3%) no endoscopic diagnosis was obtained. In only 13 inpatients, a single endoscopy was sufficient, while on 20 patients we performed two endoscopies, on ten patients three, and on 16 patients four or more endoscopic examinations or endoscopic hemostasis.

Scintigraphy was performed in 20 cases (31.7%), angiography in 14 patients (22.2 %). For four patients (6.3%) a single diagnostic intervention was sufficient, whereas 59 patients (93.7%) required several examinations (endoscopy, scintigraphy, angiography, computed tomography (CT)) (Table 3).

In 61 cases (96.8%) diagnostic localization was successful. In 41 patients (67.2%) this was achieved by endoscopy, in 12 patients (19.7%) by angiography, and in eight cases (13.1%) by scintigraphy (Table 4).

In four cases (9.8%) of endoscopy patients with the source of bleeding identified (n=41) bleeding was initially controlled, but recurred and eventually required surgery.

On 58 patients the surgical intervention (92.1%) included intestinal resection. The procedures performed included 15 sigmoidectomies (23.8%), 11 segmental small bowel resections (17.5%), 11 resections of the left hemicolon (17.5%) and ten subtotal colonic resections (15.9%), seven resections of the right hemicolon (11.1%), one proctectomy (including Hartmann's procedure) (1.6%) and five nonresecting surgeries (7.9%) (Table 5).

The complication rate for the patients under study suffering from acute lower gastrointestinal bleeding in need of transfusion and surgery was 60.3% (38 patients). Most prominent were inflammatory complications (pneumonia, peritonitis, sepsis, multiple organ failure (MOF)), rebleeding as well as direct and indirect effects of the profuse initial hemorrhage such as coagulation disorders and cardiac complications following hemorrhagic shock. Ten of the 63 patients died, i.e., the mortality rate was 15.9%.

Discussion

To this day, there is no uniform, standardized diagnostic and therapeutic path followed by all clinicians to evaluate the symptom of severe hematochezia. This is a question not only of divergent professional views on the optimum procedure, but also, to a large extent, of the availability of human and material resources. In 2007, for example, a case report was published on the use of recombinant factor VIIa to treat fulminant hematochezia secondary to Crohn's disease. Angiography to localize the source of bleeding was not available in the treating hospital.[15] Acute lower gastrointestinal hemorrhage with hemodynamic consequences is a potentially life-threatening situation that is a test of the attending physicians' experience and individual abilities. In this context, diagnosis seems to be at least as challenging as intensive care, endoscopic, or surgical therapy. Intensive discussions about the ideal diagnostic and therapeutic approach have for many years been featured in publications and on congresses. Furthermore, there are different views and procedures in the various centers, sometimes even differences within the same hospital depending on the resources and preferences of the attending physician. For example, some authors recommend an initial colonoscopy in cases of severe hematochezia,[8,11,16] while others favor an early workup of the more easily accessible upper gastrointestinal tract by gastroduodenoscopy to exclude life-threatening bleeding from esophageal varices.[5,6,17] The diagnostic path established and standardized in our institute is shown in Fig. 1; it is based on our own experience as reported in this paper as well as on evidence from the available English and German literature published over the past three decades. General adherence to this path is mainly ensured by in-house staff rotations and continuous training.

Table 3 Diagnostic Spectrum of Acute Lower Gastrointestinal Bleeding Requiring Transfusion (n=63 Patients)

Diagnostic method	Number	Percent
Physical examination, including proctoscopy and rectoscopy	62	98.4
Gastroscopy	52	82.5
Colonoscopy	45	71.4
Gastroscopy plus colonoscopy	38	60.3
Scintigraphy	20	31.7
Angiography	14	22.2

Table 4 Examination Method that Succeeded in Determining the Source of Acute Lower Gastrointestinal Bleeding (n=63 Patients)

Effective diagnostic localization method	Number	Percent
Bleeding source localized in n cases	61	96.8
Endoscopic diagnosis	41	67.2
Angiography	12	19.7
Scintigraphy	8	13.1

Table 5 Scope of Surgical Intervention Following Acute Lower Gastrointestinal Bleeding Taking into Account the Indication as Listed in Table 6 (n=63 Patients)

Surgeries performed	Number	Percent
Resection of sigmoid colon	15	23.8
Segmental small bowel resection	11	17.5
Left hemicolectomy	11	17.5
Subtotal colectomy	10	15.9
Right hemicolectomy	7	11.1
Proctectomy	1	1.6
Non-resecting surgery	5	7.9

In our institute the diagnostic-therapeutic strategy depends on the severity of gastrointestinal bleeding. To evaluate the severity, we first rely on shock room management that is based on ATLS® (advanced trauma life support) standards. Here, the stabilization of cardiopulmonary parameters including fluid substitution and, if necessary, blood transfusion, play a crucial role. After these initial measures, all pieces of evidence (patient history, clinical picture, clinical examination with rectal digital palpation, laboratory findings, circulatory parameters, etc.) together lead to a first assessment of the severity of bleeding. Where the history provides helpful indications such as, for example, in the case of a known chronic inflammatory bowel disease or an alcohol abuse history with known esophageal varices, adequate endoscopic diagnostic procedures will be initiated accordingly. If the history is of no diagnostic use, we prefer an early proctorectoscopy, which has proved to be effective in a number of cases, to the more time-consuming endoscopic diagnosis.

Endoscopic Diagnosis (Colonoscopy and Esophagogastroduodenoscopy)

In 15% of the cases, fulminant hematochezia originates from the upper GI tract, which is usually much more easily accessible for endoscopic diagnosis than the colon, which is often soiled by stool. A negative procto-rectoscopy is therefore followed by gastroduodenoscopy whenever the patient history or the clinical picture provide no further evidence suggesting bleeding from the lower gastrointestinal tract. Additionally, bleeding from the upper GI tract is often more severe and frequently life-threatening as for example in the case of bleeding esophageal varices due to portal hypertension. Aspiration of nonbloody gastric fluid does not exclude upper GI bleeding, the detection of bile in the aspirate, however, makes upper gastrointestinal bleeding seem unlikely.[18] To this day, endoscopy remains the most important diagnostic method in our hospital. Of all patients, 93.7% underwent endoscopy, 60.3% both gastroscopy and colonoscopy. The group of selected patients under review in this paper is characterized by an especially severe course of the disease, in all cases leading to a surgical intervention. This is also reflected in the observation that 73% of the cases required recurrent endoscopy and 16 patients (25.4%) needed as many as four or more examinations.

What is needed for both upper and lower emergency endoscopy is a wide lumen duct to aspirate blood, coagula, and fecal matter and the presence of at least two efficient suction systems. Furthermore, a powerful flush pump is connected to the separate water jet tube of the endoscope. These material requirements cannot, however, compensate for an examiner's lack of competence. Negative procto-rectoscopy and gastroscopy in hemodynamically stable patients will be followed by colonoscopy carried out by an experienced endoscopist. In the past, this method has proved safe and beneficial even under adverse, unclear conditions without prior intestinal lavage.[19,20] In 72% to 86% of the cases, this method led to a diagnosis when carried out by an experienced endoscopist. In cases of moderate active hemorrhage it proves more sensitive than angiography, which, in turn, is of greater use for massive active hemorrhage.[7,13,21] For the detection of angiodysplasia, colonoscopy has been ascribed a sensitivity of more than 80%.[22] In the past, considerable data have shown that early colonoscopy within 12 h after admission can significantly reduce the period of hospitalization of the patient.[13,23,24] Based on today's evidence, prompt performance of this procedure must therefore be postulated.

Angiography

Angiography has proved more sensitive to massive active hemorrhage than colonoscopy. We therefore carried out a selective angiography of the mesenteric arteries on 14 stable patients after negative colon endoscopy. Angiography is also the diagnostic method of choice for the less common acute bleeding from the small intestine which is beyond the limits of endoscopic procedures. The method is also useful for angiodysplasia because vascular anomalies are visible without extravasation of blood. Angiography detects bleeding greater than 0.5 to 2 ml/min with a sensitivity of 40% to 86% and a specificity of 100%. False-negative results are due to the intermittent nature of hemorrhage. Provocation of bleeding after failed diagnostic localization, e.g., by applying anticoagulants under controlled conditions, has been described[25] and is carried out at our hospital in strictly indicated cases. These cases include longer-term diseases with recurrent undetectable hemorrhage, especially those of clinical relevance. It must be established that angiography is an invasive examination method which in the past, especially when applied for therapeutic purposes (embolization), has been accompanied by complications such as intestinal wall necrosis. Selective catheter-based vasopressin infusion, which involves less risk, but high recurrence rates, extends the therapeutic spectrum. It was not before the option of superselective microembolization with microcoils, gelfoam, or polyvinyl alcohol particles that the risk of severe side effects could be reduced to an acceptable level,[26,27] and today it is increasingly seen as the preferred, less invasive intervention prior to surgery.[28] If the bleeding site has been detected by angiography, the selective catheter should be left in place even if embolization was ineffective. In combination with intraoperative X-ray diagnosis the bleeding site can successfully be localized for segmental intestinal resection through radiological visualization of the catheter. Stable

patients with an unidentified bleeding source are monitored in intensive care units (ICU) and re-evaluated by endoscopy and, if necessary, angiography as early as possible. For unstable patients, surgery is indicated after unsuccessful angiography.

Radionuclide Scintigraphy (Nuclear Scans)

Other than the technetium 99 colloid injection, which offers the advantage of a short half-life in vivo (little interference from background radiation) and the simultaneous disadvantage of a short diagnostic window, scintigraphy with Tc-99m-tagged red blood cells (Tc99-EC) is carried out more frequently. While this examination, which has also been carried out at our hospital (n=20), is more complex, it is beneficial in the case of intermittent bleeding requiring transfusion. With a detection threshold of approximately 0.1 ml blood loss/min, the sensitivity of this method is superior to that of angiography[29], but on account of the increasing background radiation a reliable localization is impossible after 4 to 24 h, especially with late admissions. Surgical therapy plans for segmental colon resection should therefore not be based on scintigraphy results alone.[9,30] In younger patients, scintigraphic identification of Meckel's diverticulum is a sufficient indication for surgery.

Small Bowel Evaluation (Push Enteroscopy and Capsule Enteroscopy)

To this day, hemorrhage from the small intestine remains a diagnostic challenge; if angiographic localization attempts have failed and if bleeding is intermittent, stable patients may be subjected to push enteroscopy, capsule enteroscopy, or double-balloon enteroscopy.

Push enteroscopy allows visualization and high-sensitivity evaluation of the first 50 to 80 cm of the proximal jejunum. An extra long endoscope supported by the intestinal wall is advanced distally in "caterpillar" movements. With some limitations, therapeutic intervention (hemostasis, biopsying, and resection of polyps) is also possible. Disadvantages are the risk of injury by the overtube and the incompleteness of the small-bowel evaluation. For technical and time reasons, this diagnostic procedure is unsuited in an acute bleeding situation[31,32] and has therefore not been carried out in the reviewed cases of acute hemorrhage indicated for transfusion and surgery.

For capsule enteroscopy an 11×26 mm capsule with a built-in camera is swallowed; two images per second are taken for 6 to 9 h. The location of the capsule can be reliably determined via eight electrodes attached to the patient's abdomen. Several studies have proved diagnostic superiority of this method over push enteroscopy. Disadvantages include the missing therapeutic approach, the cost, the time required, and the occasional retention of the capsule in the area of subtotal small bowel stenoses, which in 1% to 5% of the cases requires surgical recovery of the capsule.[31,33] For these reasons capsule enteroscopy plays only a minor role in the diagnosis of acute gastrointestinal bleeding.

A new and promising method is the double-balloon enteroscopy (also known as push-and-pull enteroscopy), which allows diagnostic and therapeutic exploitation of the entire small bowel. A 2-m endoscope and a flexible 1.4-m overtube allow for approximately 70% of the small bowel to be inspected within 1 to 1.5 h. By caterpillar movements, the small bowel is accordioned onto the diagnostic instrument. The therapeutic spectrum covers biopsying, resecting polypoid masses, and cauterizing bleeding lesions. Only little experience with the application of this method in an acute bleeding situation is available.[34]

Multidetector Computed Tomography

After positive reports have been published over recent years in connection with the minimally invasive multidetector CT (MDCT) and its higher sensitivity to colonic angiodysplasia compared with conventional angiography,[35,36] this type of computed tomography has also proved useful in visualizing the small bowel. This uncomplicated technique detects bleeding of approximately 0.4 ml per minute. Applied as a screening test, this procedure can therefore precede therapeutic angiography. In the future, MDCT may replace both radionuclide scintigraphy and purely diagnostic angiography in the routine management of acute gastrointestinal bleeding.[37] As early as in 2005, a report was published on the successful use of CT angiography to detect acute lower gastrointestinal bleeding, which was to be preferred over colonoscopy, angiography and scintigraphy.[38]

Treatment

In most cases (approximately 90%) of intestinal hemorrhage the source of bleeding can be identified, and in approximately 70% of the cases the bleeding can be stopped at least temporarily by endoscopic or radiological intervention. The percentage of necessary surgeries of acute colonic diverticula requiring transfusion during the same hospital stay has dropped to under 25%.[1,13] Today's reduction in surgical interventions is also reflected in the relatively low number of 63 patients that could be recruited for this paper over an observation period of 9 years.

Indications for surgical intervention are categorized into emergency indication (peracute hemorrhage), urgent indication, and semi-elective indication (Table 6).

Over the past years and decades not only the above-mentioned diagnostic procedures have clearly improved in

Table 6 Indications for Surgical Intervention at Our Hospital

Emergency intervention
Peracute bleeding
Hemodynamically instable patient
Bleeding not controllable by intervention (required transfusion volume of ≥6 PRBC units/24 h)
Urgent intervention
Continuous bleeding with effects on hemoglobin or recurrent bleeding requiring transfusion
Semi-elective intervention
Bleeding from initially surgically repairable lesion after interventional control of hemorrhage or intermediate cessation of bleeding

efficiency, but a broad range of sufficient therapeutic methods has also been refined. In the area of endoscopy, contact coagulation,[14] the epinephrine injection,[14,44] hemoclipping,[45] the application of fibrin sealant,[46] or combinations of several of these procedures have proved effective. In therapeutic angiography the option of superselective microembolization with microcoils, gelfoam, or polyvinyl alcohol particles has reduced the risk of severe side effects to an acceptable level,[26,27] and today it is increasingly seen as the preferred, less invasive intervention prior to surgery.[28] Among the nonsurgical therapies to stop bleeding from radiation proctitis, the argon laser,[48] the Nd:YAG laser,[49] and argon plasma coagulation[47] have proved effective.

Primary surgical intervention in the case of peracute bleeding as an emergency surgery is therefore an exception. More common is a surgical therapy as an urgent or early elective measure following colonoscopic or angiographic diagnosis with or without unsuccessful therapeutic intervention.

The surgical strategy depends on the intensity, cause, and localization of bleeding as well as on patient-related factors.

While prompt surgery is mandatory for peracute hemorrhage, a semi-elective surgical therapy is usually recommended after the second bleeding episode since after recurrent bleeding the probability of a third episode rises to over 50%.[43] Generally, in an acute situation with a poor general state of the patient (unstable circulation and need for catecholamine, hypothermia, poor respiratory condition, coagulation disorder, sepsis, etc.), the only surgical interventions to be performed are those indispensable for direct patient stabilization. This will usually be the suturation of the bleeding site or segmental intestinal resection. This type of damage control surgery will under certain conditions not perform anastomosis or fecal diversion initially, thereby accepting the possible necessity of a second intervention.

For stable patients we postulate one-time definitive surgical care. This objective can usually be achieved if the bleeding site is localized preoperatively or intraoperatively.

There is broad consensus today that segmental intestinal resection is justifiable only after the vascular lesion has been securely identified; "blind" segmental resection purely on suspicion is associated with a high rate of recurrent bleeding and corresponding morbidity and mortality rates. Furthermore, the prognosis deteriorates if a relaparotomy becomes necessary due to rebleeding.[2,4,13,42] In the past, several working groups have compared the results of segmental versus subtotal intestinal resection in the event of acute intestinal hemorrhage.[12,39–41] Where segmental resection was performed after successful localization of the bleeding site, the recurrent bleeding rate ranged from 0% to 14%. The lowest recurrent bleeding rate was observed after subtotal colectomy (<5%). On account of these results, some authors generally tend toward subtotal colectomy even if the source of bleeding has been identified,[39] in order to reduce lethality. However, since this measure adversely affects the quality of life especially of elderly patients on account of severe incontinence problems, we refrain from this more radical approach in initial interventions. We perform subtotal colectomies only in case of detected bleeding following colitis ulcerosa or of surgically indicated colonic hemorrhage of other genesis with no clear evidence of a focus. After successful preoperative or intraoperative localization of the vascular lesion of other genesis (diverticulum, Crohn's disease, angiodyplasia, etc.), we generally perform a segmental resection, including an initial anastomosis if the patient is stable. If neoplasia is suspected on account of endoscopic or intraoperative findings, the resection is performed in accordance with oncological criteria.

If small bowel hemorrhage has been localized (e.g. after angiography, push or double-balloon enteroscopy), the affected small-bowel segment is resected. After unsuccessful angiographic superselective embolization, the catheter may be left in place for radiological or palpatory intraoperative confirmation of the affected segment. In this situation, locoregional or systemic intra-arterial application of vasoactive substances such as vasopressin may save valuable time in unstable patients.

If the source of bleeding cannot be identified despite intraoperative intestinal incision, lavage, and careful exploration, stable patients may receive temporary fecal diversion once or twice in order to provide secure endoscopic evidence of the focus in case of recurrent hemorrhage. Alternatively, the stabilized patient may be re-evaluated postoperatively and the invasive strategy of creating a fecal diversion be dismissed. The strategy should be determined on an individual basis, taking into account the patient's wishes. Considering the above-mentioned regime, resection of the sigmoid colon was the most frequently performed intervention (Table 5). A challenging, while rare exceptional situation is massive small-bowel bleeding without localization of the focus.

There is no other solution than the time-intensive, systematic, part-by-part evaluation of the complete small bowel with multiple incisions, segmental endoscopy, and lavage.

Today, surgical intervention appears at the end of a long, ultimately unsuccessful chain of diagnostic and therapeutic interventions. Patients referred to surgery thus have clearly elevated risks. In figures, this led to a complication rate of 60.3% and a mortality rate of 15.9%. Prominent were inflammatory complications (pneumonia, peritonitis, sepsis, MOF) as well as direct and indirect effects of profuse hemorrhage (coagulation disorders, hemorrhagic shock, myocardial infarction, etc.). Six patients suffered from recurrent bleeding from anastomoses or of intestinal genesis.

Conclusions

Initial examination and stabilization of the patient is followed by early diagnostic localization. Today, we initially rely on nonsurgical control of hemorrhage by endoscopy or angiography; the indication for surgery is mainly limited to peracute, uncontrollable, and recurrent forms. In the case of surgery, segmental intestinal resection is recommended after identification of the lesion; if the site of colonic hemorrhage is uncertain, subtotal resection is the method of choice. For stable patients with unverifiable small bowel hemorrhage we recommend ICU monitoring and re-evaluation after a period of time.

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J Gastrointest Surg (2008) 12:2221–2226
DOI 10.1007/s11605-008-0537-4

Laparoscopic Segment VI Liver Resection using a Left Lateral Decubitus Position: A Personal Modified Technique

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Received: 1 February 2008 / Accepted: 14 April 2008 / Published online: 13 May 2008

Abstract
Background Laparoscopic technique for lesions located in the left liver is well described in the literature. On the contrary, the best laparoscopic approach for lesions located in the right liver, such as in segment VI, is still debated.
Aim In this article, we provide a detailed description of a laparoscopic segment VI liver resection using a left lateral decubitus position with the right side up, facilitated by a personal technique. We also discuss potential advantages and disadvantages of this procedure.

Keywords Laparoscopy · Liver resection · Hepatectomy · Left lateral decubitus · VI segment

Abbreviations

HCC	Hepatocellular carcinoma
ASA	American Society of Anesthesiology
CT	Angio-computed tomography
HCV	Hepatitis C virus
EGDS	Esophagogastroduodenoscopy

Introduction

Laparoscopic liver resection is considered a complex procedure that should be performed only by a team of surgeons experienced in both laparoscopic and hepatobiliary surgery. In fact, this approach presents unique technical challenges and anatomical difficulties especially in achieving hemostasis at the transection plane.[1] To date, most reported laparoscopic techniques of hepatic resection have mainly involved the left lateral and the anterior or the inferior segments of the right liver.[2–9] Left lateral hepatic sectionectomy (bisegmentectomy II–III), commonly performed in few limited referral centers, has been extensively described in literature and has been proposed as a routine approach for left-located lesions.[10–13] In contrast, the laparoscopic technique for segment VI resection is still a matter of debate.

The most frequently reported laparoscopic approach to segment VI resection describes the patient in a "French" supine position with the surgeon standing between the patient's legs and one assistant on each side.[7,14–17] After an early experience in which we adopted the supine position, we changed our technique, positioning the patient in a left lateral decubitus similar to the technique used to perform the right adrenalectomy.[18] In this article, we provide a detailed description of laparoscopic segment VI liver resection facilitated by a personal technique. We also discuss the potential advantages and disadvantages of this procedure.

Patients and Methods

From May 2000 to December 2006, 110 laparoscopic procedures for benign and malignant hepatic diseases were performed in the Department of General and Hepato-Pancreato-Biliary Surgery at S.M. Loreto Nuovo Hospital, Naples, Italy. Of the 110 procedures, 10 (9%) were segment

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VI resections. Indications included either liver metastases from colon cancer or hepatocellular carcinoma (HCC) in well-compensated cirrhotic patients (Child–Pugh class A). Patients with complicated cirrhosis (Child–Pugh class B–C) or an American Society of Anesthesiology classification greater than 3 were excluded. Previous abdominal surgery, including previous liver resection, was not considered a contraindication to the laparoscopic approach.

All patients were evaluated preoperatively according to a standard protocol that included blood examinations, abdominal ultrasound, and angio-computed tomography scan. We also performed a spirometry to check pulmonary function and an esophagogastroduodenoscopy (EGDS) to evaluate esophageal varices in cirrhotic patients.

Evaluation of hepatic function was done using the Child–Pugh classification for liver dysfunction. All patients with HCC had histologically confirmed cirrhosis classified according to the Ishak score for fibrosis (F 5 for one patient; F 6 for seven patients). All the lesions were localized in segment VI of the liver. We did not perform any associated procedure in this series of patients. Liver resection was defined according to International Hepato-Pancreato-Biliary Association classification using segmentectomy for the resection of the segment VI of the liver.[19]

Operative Technique

Patient Preparation and Positioning

Thromboprophylactic measures are used routinely. The stomach is decompressed with an orogastric tube, which is removed at the conclusion of the procedure. The patient is placed in a left lateral positioning (right-side up), in mild reverse-Trendelenburg position, with the operating surgeon and the assistant standing by the patient's left flank and facing the abdomen.

Port Placement

Four trocars typically are used in this procedure (Fig. 1). The trocars were positioned along a semicircular line with the concavity facing the right subcostal margin. The initial trocar is usually placed by Hasson technique, while all subsequent ports are inserted under direct vision. Rarely, in morbidly obese patients, CO_2 pneumoperitoneum is established with a Veress needle and the first port is inserted, under vision, using an optical trocar (Visiport, Tyco Healthcare, Norwalk, CT, USA). Continuous CO_2 pneumoperitoneum is induced at a pressure of 12 mmHg to prevent the risk of gas embolism. The initial incision is made approximately 1 cm in length, 5 cm below the costal margin and in the right anterior axillary line (port 1); this will be used as the optical port for the 12-mm 30° laparoscope. After inspection of the abdomen, three additional trocars are placed. The second trocar is inserted via the right flank inferior and slightly posterior to the tip of the 11th rib; it enters above the hepatic colonic flexure, which rarely requires any mobilization (port 2). The third and fourth trocars are placed more anteriorly; the first one is placed approximately 5 cm from the costal margin at the medial border of the rectus abdominis muscle (port 3), while the last one is placed 5 cm below the xyphoid appendix along the midline (port 4).[18]

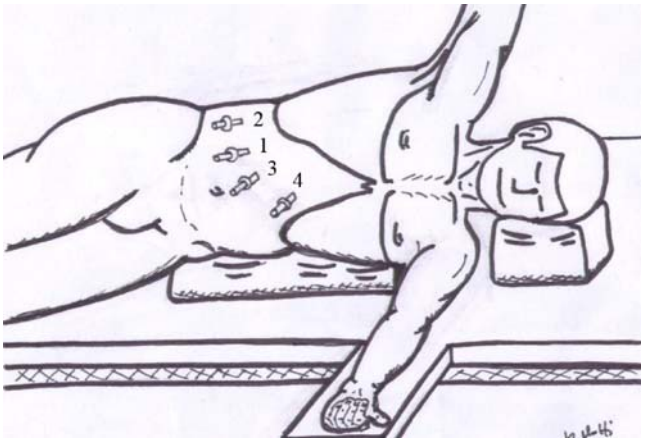

Figure 1 Port placement and patient positioning: 12-mm camera port (*1*), 12-mm surgical ports (*2* and *3*), and 12-mm port for liver retractor and hanging of the tape (*4*).

All trocars carry a 5- to 12-mm port to allow the introduction of the laparoscopic ultrasound probe, an easier change of instruments, and the use of either a 10-mm harmonic scalpel (Ultracision; Ethicon Endosurgery, Cincinnati, OH, USA) or 5/10-mm Ligasure device (Ligasure Valleylab, Boulder, CO, USA) with both the right and left hands.

Surgical Exploration and Liver Mobilization

A standard diagnostic and staging laparoscopy is performed to rule out the presence of extrahepatic malignancy or unresectable intrahepatic disease; then, the liver is examined systematically by means of intraoperative ultrasonography to confirm number, location, and extension of the lesion and its relationships with the main hepatic vascular and biliary structures and to visualize its medial margin inside the parenchyma. In the first seven cases, an Aloka transducer (Tokyo, Japan) was used, whereas in the last three patients, a trasducer from B&K type 8555 (B&K Medical System, Marlbourough, MA, USA). They offer B-mode, M-mode, spectral Doppler, and color flow monitoring. The "fan-type" liver retractor is inserted in the medial trocar (number 4) to gently reflect the right hepatic lobe

upward. The procedure starts with the laparoscope in the first trocar (number 1) while the surgeon works through ports 2 and 3.

After incision of the pars lucida of the lesser omentum, a curved esophageal retractor (Endo Retract Maxi, Tyco Healthcare) is passed through the foramen of Winslow around the porta hepatis with a vascular tape inserted in its open tip (Fig. 2). The tape can simply surround the hepatoduodenal pedicle and then be passed through a 16-F rubber drain used as a tourniquet to enable the Pringle maneuver, if necessary. At this point, the mobilization of the liver can begin; the right lateral hepatic attachment and the triangular ligament are divided using Ultracision or Ligasure devices while the round and falciform ligaments are preserved. This dissection is typically carried up to the diaphragm, allowing a more effective mobilization of the liver.

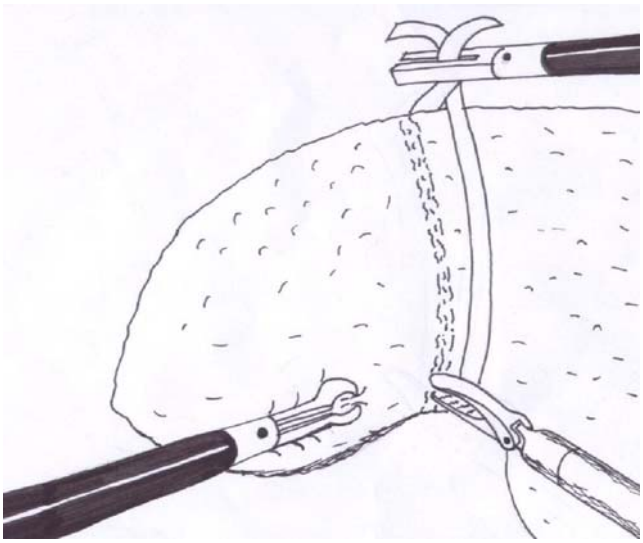

Figure 3 An umbilical tape, controlled by a grasping forceps, is passed around the right mobilized liver to lift and handle the segment VI during the parenchymal transection.

Parenchymal Transection and Specimen Removal

The extension of resection is identified by the use of ultrasonography, and the area is marked by monopolar electrocautery. Specifically, a margin distance between the lesion of interest and the cut line on the surface of the liver is precisely measured by ultrasonography: the scored capsule appears as a hypoechoic linear shadow perpendicular to the ultrasound probe and is used to verify the surgical margin's position and width from the lesion before starting the parenchymal transection. Even during parenchymal transaction, the ultrasonography is employed repeatedly to guide the transection plane (visualized as a hyperechoic line) away from the tumor margin.

It is helpful to pass an umbilical tape, controlled by a grasping instrument inserted in the medial port, around the right mobilized liver to facilitate the lifting and the handling of the segment VI (Figs. 3 and 4). The hepatic transection is then started by sectioning Glisson's capsule with the harmonic scalpel, which is able to secure vascular and biliary structures up to 3 mm; minor bleeding is managed by bipolar electrocautery forceps simultaneously employed with the ultrasonic dissector to provide liver retraction and improve hemostasis. Intraparenchimal control of major vessels, such as segment VI vascular pedicle, was achieved with surgical clips or by Ligasure device. We never used a stapling device in this series of patients. The parenchymal division is continued up to the end margin located between segments VI and VII under ultrasound control to obtain adequate negative resection margin (Fig. 5). The resected specimen is then placed in a plastic retrieval bag and removed through the slightly enlarged periumbelical inci-

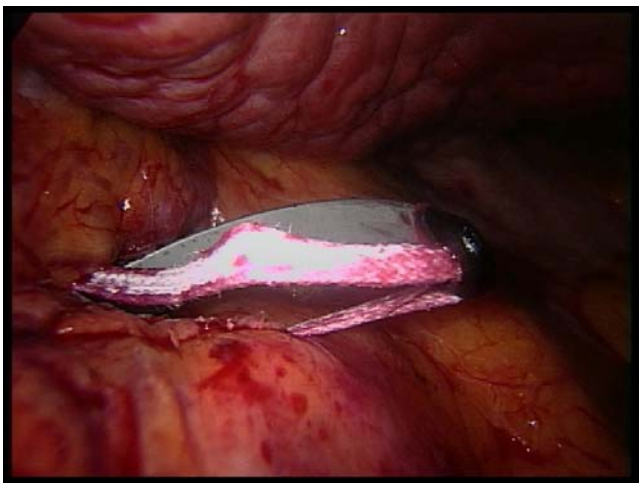

Figure 2 Preparation of Pringle maneuver with an esophageal retractor.

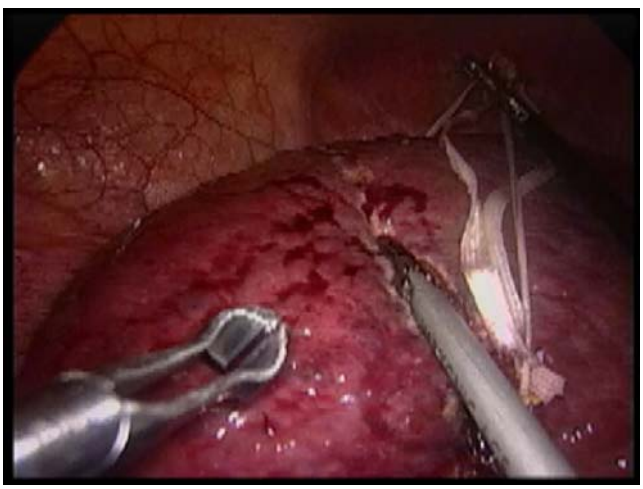

Figure 4 An umbilical tape, controlled by a grasping forceps, is passed around the right mobilized liver to lift and handle the segment VI during the parenchymal transection.

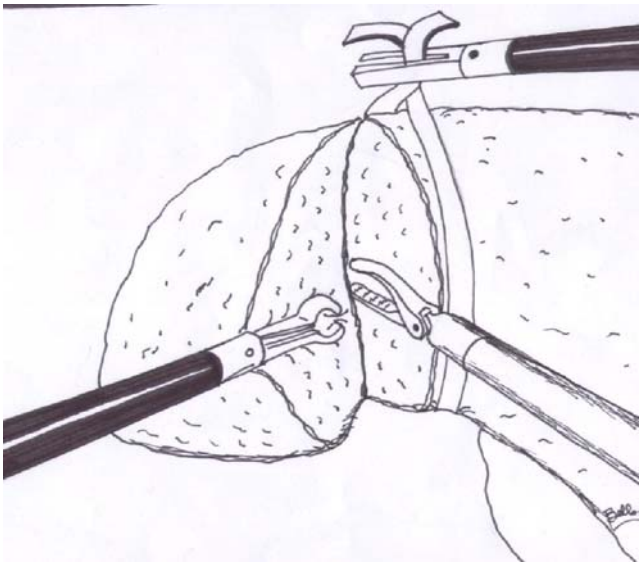

Figure 5 Parenchymal transection in an ideal orthogonal position (90°), with all the instruments in a more precise triangular position while the left hand of the surgeon is used to open the liver parenchyma.

sion or a minilaparotomy in the suprapubic or subcostal region, thus enabling histological review.

The Argon Beam coagulator (Force FX, Valleylab) was sometimes applied to control blood oozing from the transaction plane. During its use, the abdominal pressure (<15 mmHg) was carefully monitored to prevent the risk of gas embolism. All resection bed surfaces were treated with a biologic fibrin glue (Tissucol; Baxter, Vienna, Austria) or with a new hemostatic gel (Floseal; Baxter) to minimize the risk of biliary leak and to ensure hemostasis. In all cases, a drain was inserted next to the site of resection. Desufflation of CO_2 was performed before trocars WERE removed under direct vision.

Results

The mean age of the patients was 61.3 years (range, 45–72 years); six patients were male and four were female. Eight patients presented with HCC related to hepatitis C virus infection, while two patients had liver metastases from colon cancer. In three patients, EGDS provided evidence of initial oesophageal varices (grade F1).

All tumor nodules were located in segment 6 of the liver. The mean size of the lesions was 3.5 cm (range 1.3–5.2 cm). The mean number of tumor nodules resected was 1.2±0.1 (range 1–2). None of the patients had had previous abdominal operations, except for those two presenting with colorectal liver metastasis. A laparoscopic segmentectomy (segment VI liver resection) was the surgical procedure performed in all patients. The laparoscopic procedures were completed in all patients, with a mean operative time of 135 min (range 110–185 min). There were no intraoperative complications and no patients required intraoperative or perioperative blood transfusions. The Pringle maneuver was never needed. Oral intake of fluid usually started on the second postoperative day; cirrhotic patients received a low-sodium diet. All the patients were discharged home after an uncomplicated course, between postoperative days 5 and 9 (mean, 6.9 days). The surgical margins in all patients were negative and more than 1 cm. The mean follow-up period was 39.4 months (range, 14–91). To date, no intrahepatic local recurrences or port-site metastases have been observed in these oncological patients.

Discussion

Laparoscopic liver resections are currently perceived as the most complex of all laparoscopic procedures.[20] This kind of surgery is characterized by dreadful complications such as potential massive hemorrhage or the risk of gas embolism and technical difficulty of performing various surgical maneuvers laparoscopically.[1] Except resections of left lateral segments, a standardized approach to right lateral liver segments does not yet exist. To date, the most frequently reported technique of laparoscopic liver resection for segment VI lesions describes the patient in the "French" supine position with the surgeon standing between the patient's legs and with one assistant on each side.[7,14–17,21] This approach has probably been preferred by the majority of hepatobiliary surgeons because of their laparoscopic learning curve starting with a standard cholecystectomy. Similarly, we performed the two first segment VI liver resections in the more usual supine position. However, our increased experience in advanced laparoscopic surgery allowed us to be more confident with different patient's positions.

In particular, a left lateral position, which we already used to perform right adrenalectomy,[18] makes either right liver mobilization or segment VI resection comfortable. In fact, liver dissection can be easily carried out up to the diaphragm, allowing a total mobilization of the right liver to be more comfortable than with the patient in the supine position. In this step, we usually do not section the round ligament, either to save the umbilical vein in cirrhotic patients or to leave the liver fixed to the abdominal wall to facilitate the laparoscopic operative maneuvers.[12]

A shortcoming we observed with the patient standing in left lateral decubitus was that we had to pass a tape around the porta hepatis to perform a Pringle maneuver. Anyway, the use of an esophageal retractor always made the preparation of the Pringle possible, even if it was just a preventive surgical step. In fact, we always try to avoid this maneuver, even in cirrhotic patients.[9,22]

A well-recognized drawback of the laparoscopic approach is surely the lack of manipulation that may be essential for a precise and safe liver parenchymal transection, with consequently low intra- and postoperative bleeding. To overcome this problem, we recommend performing the parenchymal division making a large use of the intraoperative ultrasound to control both the line of resection and the relationship between the tumor and the major vascular structures. Furthermore, in this step, we found it very helpful to use a retraction tape circling the mobilized right liver to assist with the hepatic transection. The liver can be better managed by this technique and oriented towards the dissecting instruments, allowing a more precise line of resection.

A potential advantage of the left lateral decubitus position is that the entire intestine, including the hepatic colonic flexure that rarely requires any mobilization, falls downwards. Therefore, the instruments held by the left hand of the surgeon can be used to open the liver parenchyma, instead of managing the intestine.

Lastly, one potential technical advantage is the surgeon facing the patient's abdomen and performing the liver transection in an ideal laparoscopic orthogonal position (90°), with all the instruments in a more precise triangular position. In this setup, we were able to continue the hepatic resection under ultrasound control,[23,24] up to the end margin located between segments VI and VII, performing a comfortable hepatectomy and achieving a good hemostasis of the transection plane. On the contrary, the hemostasis of the transection plane, especially at the end margin, was difficult in the two early patients operated on in the supine position, probably due to the tangential position of the dissecting instruments.

In this series, we were never compelled to convert to open surgery, though we think this position does not represent an obstacle. In fact, in case of uncontrolled hemorrhage, a subcostal incision incorporating the port sites can be quickly performed, allowing good exposure of the operating field even in lateral position. Otherwise, in controlled conversion, it is possible to reposition the patient in the supine position before performing open laparotomy if necessary. Previously, a few authors reported on the use of left lateral decubitus position to perform a segment VI liver resection but without describing the personal technique.[5,25]

Although we have not compared this new method with the technique performed in the standard supine position, it seems to be a comfortable option for segment VI liver resection, even in cirrhotic patients. The potential advantages and disadvantages of these two techniques should be evaluated in a comparative study on a large number of patients to suggest one technique as being superior to the other.

In conclusion, we described a personal modified technique as a suitable choice for patients with isolated lesions located in segment VI, if performed in highly specialized units, by surgeons assisted by all requested technologies and with extensive experience in hepatobiliary and advanced laparoscopic surgery.

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J Gastrointest Surg (2008) 12:2227–2230
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Local Resection of the Pancreatitic Head for Pancreatic Pseudocysts

Kevin E. Behrns

Received: 5 February 2008 / Accepted: 2 May 2008 / Published online: 3 June 2008

Abstract
Background Local resection of the head (LRPH) has improved markedly the clinical outcome of patients that undergo surgery for chronic pancreatitis. LRPH is often combined with a lateral pancreatojejunostomy for complete duct drainage. Randomized controlled trials have confirmed the superiority of the Frey and Beger operations compared to pancreatoduodenectomy. Appropriate patient selection is critical to an excellent outcome. Patients with an enlarged pancreatic head or duodenal or biliary obstruction are ideal candidates for LRPH. In addition, patients with symptomatic pseudocysts in the pancreatic head can be adequately treated with these operations.
Procedure The procedure described herein includes a generous pancreatic head resection to ensure pain relief, a pancreatic ductotomy onto the body and tail of the gland for complete drainage, and an intrapancreatic biliary sphincteroplasty for decompression of an obstructed bile duct.
Conclusions Perioperative hemorrhage is a potential major complication associated with LRPH. The long-term outcome is an excellent pain relief and improves overall quality of life.

Keywords Chronic pancreatitis · LRPH · Pseudocyst · Techniques

In the last two decades, several operative variants of local resection of the pancreatic head (LRPH) have been introduced and popularized as preferred treatments for patients with severely symptomatic chronic pancreatitis. The benefits of LRPH for chronic pancreatitis have been well documented in prospective, randomized controlled studies. [1] The advantages of these operations compared to pancreatoduodenectomy include decreased morbidity, less pain, and improved quality of life. [1] Furthermore, the type of local pancreatic resection, the Beger or Frey procedure, appears to have little influence on outcome with both procedures providing excellent results. [2] While the benefits of these operations have been extolled for chronic pancreatitis, little is written about the value of LRPH for chronic pancreatitis complicated by pseudocysts located in the head of the gland (Fig. 1). Pancreatic pseudocysts accompany chronic pancreatitis in nearly 40% of patients, but many of these pseudocysts are small and asymptomatic. However, symptomatic pseudocysts arising in chronic pancreatitis may cause significant symptoms and adjacent organ compromise such as biliary or gastroduodenal obstruction or venous thrombosis. Because the pancreatic duct in chronic pancreatitis may be significantly strictured or obliterated, endoscopic treatment may not be possible. In addition, lateral pancreatojejunostomy may not adequately address the neurogenic pain caused by pancreatic head enlargement. Therefore, LRPH provides a definitive approach not only for the pain caused by pancreatic head enlargement but also pain induced by the pseudocyst.

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Patient Selection

The optimal patient for a LRPH has well-established chronic pancreatitis with symptoms that are not controlled by nonoperative management including alcohol abstinence,

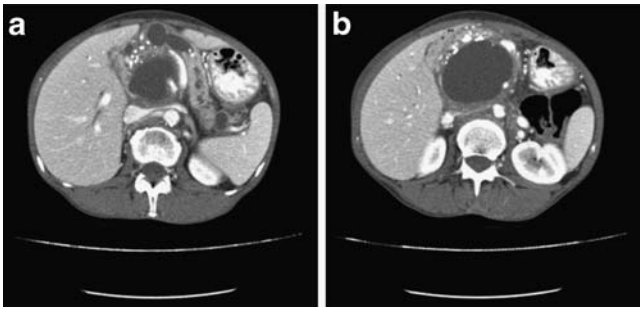


Figure 1 **a** Computed tomography scan demonstrating a pancreatic pseudocyst posterior to the head of the gland. **b** The pancreatic head contains multiple calcifications and the pseudocyst displaces the splenic vein.

pain control, pancreatic enzyme replacement, antioxidant therapy, or endoscopic treatment. Patients that have an enlarged pancreatic head on cross-sectional imaging are ideal candidates as are patients with duodenal or biliary obstruction. A preoperative endoscopic retrograde cholangiopancreatography with biliary stent placement can facilitate intraoperative identification of the intrapancreatic bile duct for the biliary sphincteroplasty portion of the operation. In addition, patients with sudden changes in symptoms such as weight loss should be thoroughly evaluated for the presence of pancreatic cancer. Patients with chronic pancreatitis complicated by pseudocysts, especially in the head of the pancreas, also may benefit significantly from pancreatic head resection combined with lateral pancreatojejunostomy. This procedure may provide relief not only of the symptoms induced by the pseudocyst but also those symptoms induced by the underlying duct pathology. Simple cystenterostomy does not address the underlying pancreatic duct pathology and may not prevent pseudocyst recurrence or provide lasting relief (Table 1).

Operative Procedure

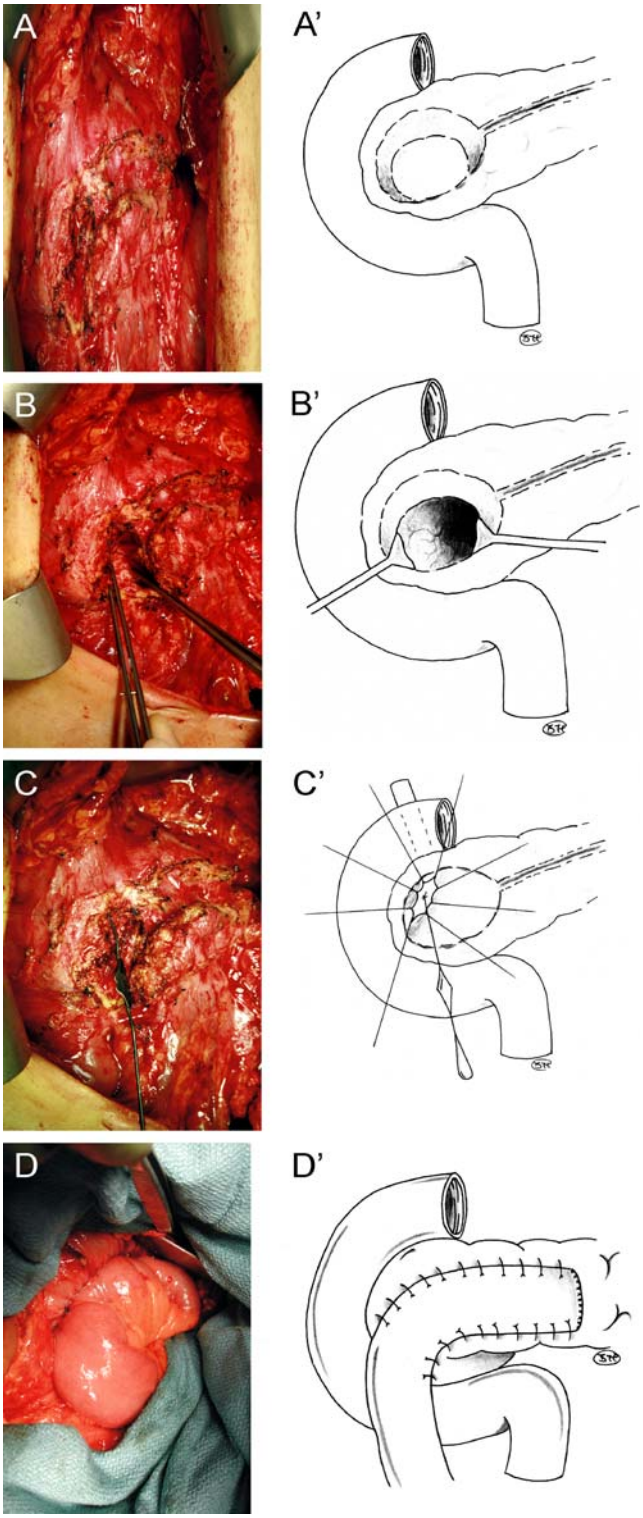
Adequate exposure of the pancreas and an associated pseudocyst is accomplished through a xiphoid to infraumbilical midline incision, wide exposure of the pancreas through the lesser sac, and a generous Kocher maneuver. Careful exposure of the pancreatic head by separating an inflamed mesentery, identifying the superior mesenteric vein (SMV) and dividing the gastrocolic trunk provides excellent exposure for ample resection of the pancreatic head. Identification and separation of the SMV from the head of the pancreas is important to gain wide exposure of the pancreatic head and uncinate process. The SMV should be cleared anteriorly and laterally up to the inferior border of the pancreas such that its location and course are noted to prevent injury to the vein. However, its course beneath the pancreas need not be exposed because of the risk of venous injury. In addition, the distal stomach and proximal duodenum should be freed from the pancreas, and the gastroduodenal artery could be controlled superior to the pancreas. The remainder of the operation consists of the pancreatic head resection, ductotomy of the neck, body, and tail of the gland, and an intrapancreatic biliary sphincteroplasty.

The pancreatic head is resected leaving only a thin (5 mm) rim of pancreas attached to the duodenum (Fig. 2). The resection should extend from the medial aspect of the duodenum to the right of the SMV and pancreatic neck in the transverse direction. Longitudinally, the resection should extend from the entry of the gastroduodenal artery into the pancreas and to the anterior portion of the pancreas as it becomes the uncinate process. A 3–5-mm thickness of the gland is all that remains as the posterior surface of the pancreas. Extensive pancreatic head resection is an important component that leads to excellent long-term relief of pancreatic pain. [3] Bleeding during the resection is con-

Table 1 Overview of All Patients with Symptomatic DD

Patient	Location of DD	Complication	Treatment
1	Segments III–IV	Acute retroperitoneal perforation	Segmental duodenectomy
2	Segment III	Acute retroperitoneal perforation	Pylorus-preserving duodeno-pancreatectomy (pp-Whipple)
3	Segment II	Chronic complaints and recurring episodes of fever	Excision of the diverticula
4	Segment II	Chronic biliary and pancreatic obstruction with chronic-atrophic pancreatitis	Pylorus-preserving duodeno-pancreatectomy (pp-Whipple)
5	Segment III	Small iatrogenic perforation caused by an ERCP (biliary obstruction)	PTCD, period of parenteral nutrition and antibiotics
6	Segment II	Hemorrhage (CHILD C hepatopathy)	Conservative, fresh frozen plasma
7	Segment II	Infection and biliary obstruction	ERCP with papillotomy and insertion of an naso-biliary tube, antibiotics
8	Segment II	DD infection with biliary obstruction and cholangitis	ERCP with papillotomy and insertion of an naso-biliary tube, antibiotics

DD Duodenal diverticulum, *PTCD* percutaneous transhepatic cholangio-drainage, *ERCP* endoscopic retrograde cholangiopancreatography



◀ **Figure 2** Intraoperative photographs and paired correlative drawings demonstrating the components of LRPH. **a**, **a′** In this patient with a posteriorly based pancreatic head pseudocyst, the pancreatic duct was opened in the body of the pancreas, and the ductotomy was extended toward the head of the gland. **b**, **b′** The duct-to-pseudocyst communication was identified, and the pseudocyst was entered and unroofed. **c**, **c′** The intrapancreatic bile duct was opened longitudinally (probe), the stent was removed, and the intrapancreatic biliary sphincteroplasty is completed by sewing the bile duct circumferentially to the surrounding pancreatic parenchyma with interrupted sutures. **d**, **d′** A side-to-side Roux-en-Y pancreatojejunostomy is created to restore pancreatobiliary–intestinal continuity.

trolled with precise suture ligation using 5–0 polypropylene sutures.

Within the pancreatic head, the pancreatic duct is identified and opened from the duodenum over the neck and onto the body and tail of the gland. All pancreatic stone material is removed. Although the duct need not be opened its entire length, the duct should be widely patent from the duodenum to the tail of the gland.

The intrapancreatic biliary sphincteroplasty is facilitated by the palpation of the biliary stent. The bile duct is opened longitudinally over the stent, and the stent is removed. The bile duct is opened superiorly until it easily accepts a 5–7-mm probe. The bile duct is tacked circumferentially to the surrounding pancreas with interrupted 6–0 polydioxanone sutures. This completes the intrapancreatic biliary sphincteroplasty, which provides excellent relief of an associated biliary stricture.

A Roux-en-Y jejunal loop is then sewn in a side-to-side fashion to the edges of the pancreas surrounding the resection and ductotomy. A jejunojejunostomy is created 50 cm distal to the pancreatojejunostomy.

The presence of a pancreatic pseudocyst changes the operative approach slightly. A portion of the pseudocyst wall should be routinely sent for histolopathologic examination. When a pseudocyst is present anteriorly in the head of the pancreas, it should be unroofed prior to the resection of the gland. A duct to pseudocyst connection should be identified and used as a landmark to open the pancreatic duct widely. The head of the gland can then be resected once intrapancreatic landmarks are identified. When a posteriorly located pseudocyst is present in the pancreas, the duct should be identified in the body or tail of the gland and opened toward the head until the duct enters the pseudocyst (Figs. 1 and 2). The pseudocyst should be unroofed, and the head should then be resected. The intrapancreatic biliary sphincteroplasty can be completed following resection.

Potential Complications

Intraoperatively, proper attention to hemostasis is critical since bleeding can be a major complication. The gastroduodenal artery must be controlled prior to the resection, and intrapancreatic bleeding during the resection should be controlled by suture ligation. Identification of a pseudoa-

neursysm on the preoperative computed tomography should lead to preoperative embolization of the involved vessel. Anastomotic leaks from the pancreatojejunostomy are uncommon because of the firm texture of the fibrotic pancreas.

Acknowledgement I wish to thank Brian Houston for the excellent graphic representations of the operation.

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J Gastrointest Surg (2008) 12:2231–2239
DOI 10.1007/s11605-008-0525-8

Surgical Therapy of Pancreatic Pseudocysts

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Received: 5 February 2008 / Accepted: 26 March 2008 / Published online: 7 May 2008

Abstract
Background Pancreatic pseudocysts are a common complication associated with acute and chronic pancreatitis. Fifteen percent and 40% of patients diagnosed with either acute or chronic pancreatitis, respectively, develop pseudocysts (Grace and Williamson, *Br J Surg*, 80:573–581, 1993). The treatment of pancreatic pseudocysts has evolved since the early 1980s, and changes in management have lead to an improved understanding of the pathophysiology of pseudocysts as well as necessary treatment paradigms.
Conclusions It has become evident that not all pseudocysts are equal. Pseudocysts arising in the setting of acute pancreatitis have a different pathophysiologic basis than those arising from chronic pancreatitis. Moreover, even those pseudocysts that arise in acute pancreatitis exhibit unique features. Pseudocysts that develop from a mild episode of pancreatitis, complicated by pancreatic duct disruption, differ significantly from those developed as a consequence of severe acute necrotizing pancreatitis with severe distortion of the pancreatic parenchyma or pancreatic duct. This review will focus on the surgical therapy of pancreatic pseudocysts in the context of the underlying pathophysiology and alternative nonoperative therapies.

Keywords Pancreatic pseudocyst · Acute pancreatitis · Diagnostic evaluation · Chronic pancreatitis

Pseudocyst versus Acute Fluid Collection

Pancreatic pseudocysts result when excessive pressure within the pancreatic duct causes duct disruption and permits the extravasation of enzyme-rich pancreatic fluid. In 1992, the *International Symposium on Acute Pancreatitis* formulated the following definition: "A pancreatic pseudocyst is a collection of pancreatic juice enclosed by wall of fibrous or granulation tissue which arises as a consequence of acute pancreatitis, trauma, or chronic pancreatitis".[2] Because pancreatic fluid is encapsulated by fibrous tissue, a pseudocyst forms over several weeks as fibroblasts react to inflammation and lay down extracellular matrix proteins. Therefore, a pseudocyst matures over a 4- to 6-week period by which time the fibrous wall thickens and achieves near-maximal strength. In contradistinction, an acute fluid collection arises in the setting of acute pancreatitis and is characterized by a collection of nonenzymatic fluid that is the result of the acute inflammatory response but not a complication of a disrupted pancreatic duct (Fig. 1). The distinction between a pseudocyst and an acute fluid collection is critical because an acute fluid collection invariably resolves spontaneously as the inflammatory process wanes. Therefore, an acute fluid collection requires no treatment, whereas a pseudocyst may resolve, persist, or enlarge over time and cause complications.

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Etiology and Pathogenesis

Pancreatic pseudocysts develop in chronic pancreatitis (40%) more commonly than in acute pancreatitis (15%); however, many of the pseudocysts in chronic pancreatitis are small, cause few if any symptoms, and, thus, require no treatment.[3] The pathogenesis of pseudocyst formation in acute and chronic pancreatitis differs significantly, and

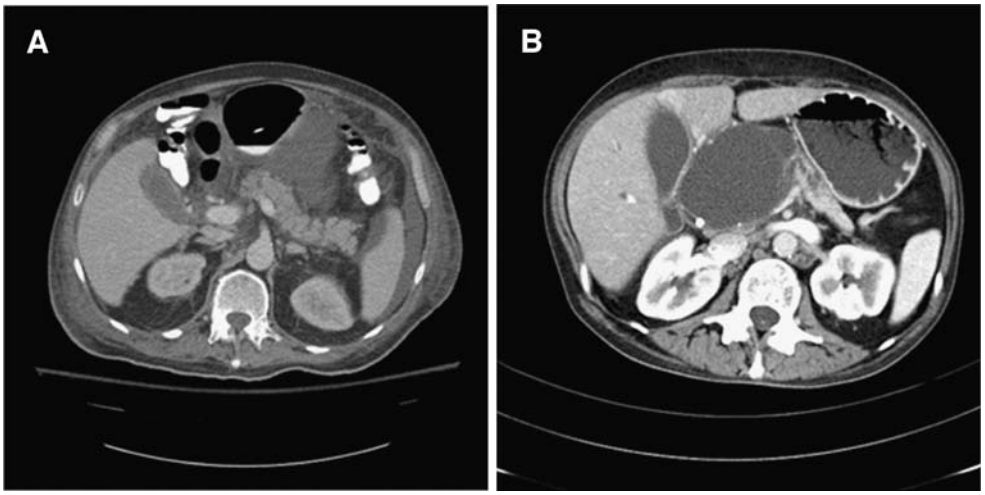

Figure 1 Computed tomography images of an acute fluid collection (**a**) and a pancreatic pseudocyst (**b**). Note the well-developed fibrous wall of the pseudocyst in contrast to the indistinct border of the fluid collection.

careful consideration of this crucial distinction is important in determining treatment options. In acute pancreatitis, most often caused by gallstones or sporadic alcohol ingestion, the pancreas has not been previously injured and has normal pancreatic duct architecture. Consequently, the main pancreatic duct (or branch duct) is often normal or has a single point of disruption that may heal well with minimal intervention. Chronic pancreatitis, however, is a unique disease in which repetitive alcohol use causes loss of acinar cells, pancreatic stellate cell activation, and the deposition of collagen.[4] This chronic, injurious process results in major changes to the architecture of the pancreas and, especially, the pancreatic duct, which may be strictured, dilated, or obliterated. Therefore, the treatment of a pseudocyst in the setting of chronic pancreatitis may differ significantly from that of a pseudocyst identified in acute pancreatitis.

In addition to distinguishing pancreatic pseudocysts in acute and chronic pancreatitis, pseudocysts must be differentiated from other cystic lesions of the pancreas, which constitute approximately 15% of all pancreatic cysts.[5] Benign simple cysts are uncommon, but because of improved cross-sectional imaging, cystic neoplasms of the pancreas are being identified with an increasing frequency and must be discriminated from pseudocysts. Cystic neoplasms are not associated with a history of pancreatitis and may contain septa, have exuberant calcium-containing wall growth, and are lined with epithelia that may undergo malignant transformation. Obviously, histologic assessment is mandatory when a pseudocyst cannot be confidently distinguished from a pancreatic cystic neoplasm.

Clinical Manifestations of Pseudocysts

Nearly 25% of pseudocysts will be less than 6 cm in size and present no symptoms.[3,6,7] Large pseudocysts may be associated with abdominal pain, nausea, vomiting, bloating, and other nonspecific symptoms. Moreover, pseudocysts may cause complications that result in a myriad of clinical presentations. For example, as pseudocysts increase in size, and gastroduodenal obstruction may be manifested by early satiety, nausea, or vomiting. A pseudocyst located in the pancreatic head may cause biliary obstruction with jaundice or even cholangitis. Pseudocysts may also cause vascular compromise with thrombosis of the splenic, superior mesenteric, or portal veins that result in venous congestion and, on occasion, gastrointestinal bleeding.[8] Pseudocyst erosion into an artery may also cause massive, difficult-to-control bleeding, including hemosuccus pancreaticus. Not infrequently, pseudocysts become infected and require drainage to prevent sepsis. Free rupture of a pseudocyst into the peritoneal cavity is rare but can ultimately cause a pancreatic fistula that is accompanied by abdominal bloating, ascites, weight loss, and fatigue.

Diagnostic Evaluation

In the past two decades, improved cross-sectional imaging has significantly enhanced acuity in the evaluation of cystic lesions of the pancreas. However, many pancreatic cystic lesions, especially those 2–3 cm in size, remain a diagnostic dilemma because of their nonspecific features. Typically, pseudocysts are discovered by either ultrasonography or computed tomography (CT) performed for the evaluation of abdominal symptoms. Refinements in imaging techniques, particularly thin-sliced, multidetector CT, permit detailed images that suggest unique cystic or pancreatic parenchymal features allowing for an accurate diagnosis. Occasionally, differentiating pure cystic lesions from combined solid/cystic lesions are problematic, and magnetic resonance imaging (MRI) with T_2-weighted sequences will clearly demonstrate cystic, fluid-filled components of the lesion. MRI also has the distinct advantage of cholangio-

pancreatography that may demonstrate a cyst–pancreatic duct communication, which may be seen in pancreatic pseudocysts or intraductal papillary mucinous neoplasms. Endoscopic ultrasonography (EUS) also displays an enhanced visualization of pancreatic cysts. This technique provides a close, detailed view of cysts, with accompanying irregularity or fine septa within the cyst wall or cyst, respectively. Furthermore, fine-needle aspiration (FNA) of cystic fluid permits evaluation for cytology, tumor markers, mucin, and pancreatic enzymes. Typically, FNA of a pancreatic pseudocyst would be acellular or demonstrate reactive cells, have low viscosity, and contain no mucin but exhibit a high amylase concentration. Evaluation of tumor markers from pancreatic pseudocyst fluid reveals a low carcinoembryonic antigen concentration, and an elevated CA19-9 concentration. Although the concentration of CA19-9 may range from 225 to 150,000 U/mL, this tumor marker does not discriminate pseudocysts from other potentially malignant cystic neoplasms of the pancreas.[9–11] Finally, for small pancreatic cystic lesions, serial imaging can accurately detect an incremental size increase, which may be an important factor in management.

Management Options

Prior to the 1970s, the treatment of pseudocysts was often empiric due to the lack of natural history data. In 1979, however, Bradley et al. published the initial study examining the natural history of pancreatic pseudocysts and found that in 54 patients under serial observation, the risk of complications from an untreated pseudocyst increased greatly after a 7-week period of observation.[12] This risk of complication from untreated pseudocysts (46%) was far greater than the risk of operative treatment. Therefore, for the next decade, pseudocysts that had not resolved by 6 weeks underwent operative therapy with the goal of enteric drainage. Outcomes from this period suggest that the overall mortality (7%) and morbidity rates (>40%) were relatively high.

Surgical therapy of pseudocysts predominated until the early 1990s when two surgical studies suggested that the risk of complication from a pseudocyst was related to the size of the lesion. At this time, pseudocysts were readily identified and followed by CT, and Yeo et al. and Vitas and Sarr found that the observation of asymptomatic pseudocysts less than 6 cm in size infrequently resulted in complications.[2,3,6,7,12–22] In fact, in the study of Vitas and Sarr, seven patients with pseudocysts greater than 10 cm were successfully managed by observation. As a result of these publications, an expectant approach to the management of asymptomatic, small pancreatic pseudocysts was prevalent and has since withstood the test of time.

The period of minimal intervention for moderate-to-large sized pseudocysts, however, was relatively brief because of the introduction of percutaneous drainage of pseudocysts and acute fluid collections.[23] For a decade or more, this procedure was performed on numerous patients with little regard for an adherence to a strict definition of a pseudocyst versus an acute fluid collection. Little recognition existed that the pathophysiology of pseudocyst formation in acute and chronic pancreatitis differed. Thus, many patients underwent percutaneous drainage of pseudocysts, and predictably the outcome was variable as more than 30% of patients subsequently required operative therapy.[3,19] With the realization that poor results accompanied the use of percutaneous drainage in unselected patients and the more frequent use of pancreatic duct imaging, medical and surgical pancreatologists have based treatment paradigms on the etiology of pancreatitis, status of the pancreatic duct, pancreatic parenchyma, and the patient's comorbid conditions.

Recently, evaluation and management of pancreatic pseudocysts began with the identification of the cause of pseudocysts (acute vs. chronic pancreatitis and symptom assessment). Although large, asymptomatic pseudocysts may be managed by observation. The risks of insidious complications such as venous thrombosis have not been documented, and, therefore, a further study of the role of observation in these seemingly asymptomatic pseudocysts is warranted. In symptomatic patients with chronic pancreatitis, careful examination of the cause of the symptoms (infection, gastroduodenal or biliary obstruction, venous thrombosis, fistula, rupture) should be sought, and cross-sectional imaging with CT or MRI is necessary. Because patients with chronic pancreatitis often have pancreatic duct strictures, imaging of the pancreatic duct is mandatory. This may be accomplished with magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). With the information from these two studies, medical and surgical pancreatologists can cooperatively create a comprehensive management plan. The management approach depends on the location of the pseudocyst as well as the duct status. Either endoscopic drainage under endoscopic ultrasonographic guidance or surgical drainage may be appropriate. Alternatively, surgical enteric drainage is preferable for giant pancreatic pseudocysts (>15 cm) or pseudocysts not amenable to endoscopic drainage. Percutaneous drainage is rarely appropriate for pseudocysts resulting from chronic pancreatitis.

The recent study by Nealon and Walser demonstrated the importance of ERCP in the definition of pancreatic ductal anatomy.[21] The study identified seven variants of pancreatic ductal anatomy and determined the results of treatment based on pancreatography. Patients with duct strictures, duct–cyst communication, and duct cutoff fared poorly with

percutaneous drainage, and the authors suggest that these patients are appropriately treated by surgical intervention. Because ERCP is invasive, however, recent studies have examined the role of MRCP and found that sensitivity of MRCP for the detection of pseudocysts is good but identification of duct–pseudocyst communication is suboptimal.[24] Appropriate management of pseudocysts may be based on MRCP findings when examined in the context of CT or sonographic findings of the pancreatic parenchyma. MRCP, however, does not delineate pancreatic duct side branch changes well, and interpretation in a heavily calcified gland may be difficult.

In the last several years, endoscopic management of pancreatic pseudocysts has become a primary mode of treatment.[13–16] Two basic endoscopic approaches may be considered: (1) endoscopic transmural drainage and (2) transpapillary drainage. Transmural drainage is indicated when the pseudocyst deforms the gastric or duodenal wall that can be punctured easily. This method depends on the Seldinger technique of dilating a track between the pseudocyst and alimentary tract lumen. EUS, which can detect wall thickness, the vascular anatomy, and the extent of pseudocyst debris, is helpful in predicting the efficacy of endoscopic transmural drainage. Transpapillary drainage may be indicated in moderate-sized pseudocysts with duct–cyst communication. Extensive necrosis is a contraindication for this method.

Symptomatic patients with large pseudocysts that are treated appropriately should experience relatively expeditious relief of symptoms with excellent long-term outcomes. Patients exhibiting symptoms that have acute pancreatitis complicated by pseudocysts and associated with a normal pancreatic duct have good outcomes with endoscopic treatment by transpapillary drainage (cyst–duct communication identified) or transmural drainage (cyst–duct communication not evident). Alternatively, pancreatic pseudocysts that arise in the setting of chronic pancreatitis characterized by parenchymal and duct changes respond best to surgical drainage by cyst-enteric anastomosis, pancreatojejunostomy, or duodenal-sparing head resection. At least 85% of patients treated by these methods should achieve good long-term results in the absence of alcohol consumption.

Percutaneous drainage is the treatment of choice for infected pancreatic pseudocysts that contain air, are associated with sepsis, and do not have extensive accompanying pancreatic necrosis.

Surgical Approaches

For decades, surgical internal drainage of pseudocysts led to the best long-term results. In recent studies, however, endoscopic drainage resulted in a 71% success rate in the treatment of pseudocysts.[16] Therefore, surgeons often treat the most complex pseudocysts that are associated with pancreatic duct changes in chronic pancreatitis. These include giant pseudocysts, multiple pseudocysts, and pseudocysts accompanied by multiple pancreatic duct abnormalities including strictures, stones, and duct cutoffs. Traditional enteric methods including cystgastrostomy, cystduodenostomy, and Roux-en-Y cystjejunostomy remain appropriate, but other options include lateral pancreaticojejunostomy, duodenal-sparing pancreatic head resection with pseudocyst incorporation with or without accompanying pancreatic duct drainage, and infrequently, pancreatic resection. Surgical approaches should consider not only pseudocyst drainage but also the definitive treatment of chronic pancreatic pain. Internal drainage has long-standing good results, but patients with chronic duct changes can experience recurrent pseudocysts, and in these patients with chronic disease, a more definitive duct procedure is attractive for those patients who have maintained abstinence from alcohol. Recent evidence suggests that lateral pancreaticojejunostomy alone (without pancreatic pseudocyst drainage) is adequate surgical management for patients with chronic pancreatitis complicated by pseudocysts.[21] Past work has shown good pain relief results with duodenal-sparing pancreatic head resections, but these operations have not been adopted widely.[17,25]

A distinct advantage of surgery, either open or laparoscopic, compared to nonsurgical, interventional management is the ability to obtain tissue from the pseudocyst wall. Improved imaging has identified increasing numbers of cystic lesions of the pancreas, and appropriate management is based on a definitive diagnosis. Histologic assessment is the only method with a diagnostic accuracy near 100% for pseudocysts. Therefore, in the appropriate clinical setting, when the diagnosis is indeterminate, a biopsy must be obtained. Furthermore, all patients undergoing operative management of pseudocysts must have intraoperative, histologic confirmation that the cyst wall lacks an epithelial layer.

A brief summary of the indications and caveats of some of the most commonly performed surgical procedures follows.

External Drainage

Operatively placed drains for the treatment of a pancreatic pseudocyst is an uncommon procedure. Infection of a pseudocyst is the primary indication for drainage, and most infected pseudocysts can be accessed percutaneously. Anatomical considerations rarely necessitate surgically placed drains, and if operative drainage is necessary, careful assessment of the extent of necrosis is necessary to ensure that formal pancreatic debridement is not required. Often, drains can be removed in 2–4 weeks depending the on the underlying pancreatic pathology and status of the pancreatic duct.

Internal Drainage

Cystgastrostomy, cystduodenostomy, and cystjejunostomy have traditionally been the most common surgical approaches for the internal drainage of pseudocysts. Endoscopic drainage by transgastric or transduodenal approaches is now commonly employed and has supplanted the need for an open operation. However, pseudocysts that do not efface the gastrointestinal lumen are not ideal for endoscopic drainage and may require open or laparoscopic approaches. It is important to note that dependent drainage is a key operative principle in large pseudocysts with caudal extension. These procedures are straightforward and provide good long-term symptom relief.

Laparoscopic Approaches

Laparoscopic surgery of the pancreas along with pancreatic pseudocyst treatment paradigms have changed significantly over the past decade. Numerous laparoscopic procedures for the treatment of pancreatic pseudocysts have been explored and successfully described in the literature.[26–31] Debate continues over which procedures can be safely and adequately performed and, more importantly, which procedures benefit the patient when performed laparoscopically.

The most commonly described laparoscopic techniques for pancreatic pseudocyst internal drainage are pancreatic pseudocyst gastrostomy through the lesser sac approach, a combined laparo-endoscopic intragastric pancreatic pseudocyst gastrostomy, pancreatic pseudocyst gastrostomy via an anterior approach, and a pancreatic cyst jejunostomy.[32–40] The largest series of therapeutic laparoscopic pancreatic cases reported by Drs. Park and Henniford were not able to reach any definitive conclusions regarding the choice of laparoscopic approach nor which patients or pancreatic conditions are best suited to laparoscopic techniques. More importantly, they were able to suggest that these new laparoscopic procedures can be reproducible, feasible, and practical to surgeons that have these techniques in their armerantrium in well-selected patient populations.[36] Hence, when a CT or endoscopic-guided percutaneous drainage fails secondary to cyst recurrence, bleeding, stent dislodgment, kinking, perforation, and clogging with viscous cyst fluid and tissue debris, a definitive yet minimally invasive approach can still be deployed in this subset of patients.[41,42]

In the lesser sac pancreatic pseudocyst posterior wall gastrotomy approach, which has been well described by a number of authors,[29–31,34–37,40] a window is created in the gastrocolic omentum through which the lesser sac is entered. The posterior gastric wall/cyst interface is appreciated, and a psueudocystotomy is performed adjacent to the corresponding posterior gastric wall. A similar gastrotomy allows the introduction of a laparoscopic stapling device. A common channel is created with the stapler. The cyst-gastric opening is then sutured. The clear advantages of this approach include the avoidance of an anterior gastrotomy. Conversely, the anterior approach requires an anterior gastrotomy which is often created over the bulge of the pseudocyst, allowing the surgeon to localize the pseudocyst by vision, palpation, or the insertion of an aspirating spinal needle. The posterior gastric wall is then opened into the pseudocyst, and the fluid from the pseudocyst is fully aspirated and examined for pathological analysis along with a portion of the pseudocyst wall. Necrotic tissue within the pseudocyst is removed and placed into a laparoscopic impermeable bag. The pseudocyst is secured to the gastric wall using either a laparoscopic stapler or sutures. The anterior gastrotomy is then closed using a linear cutting stapler or sutures.

Recently, some authors have describe a combined laparo-endoscopic–intragastric–pancreatic pseudocyst gastrostomy using both intraperitoneal and intragastric visualization to place two or three laparoscopic balloon trocars directly through the abdominal wall into the stomach.[32,33,36,38,39] The trocars are placed and spaced several centimeters apart along the greater curve of the stomach. A posterior gastrotomy into the pseudocyst is created, and after complete drainage and cyst wall biopsies, the cyst gastrostomy is extended to 3–4 cm. It is then sutured or stapled to keep the newly created lumen patent. The trocars are pulled from the anterior gastric wall but allowed to remain within the peritoneal cavity to aid in closure of the small gastrotomies.[32,33,36,38,39]

Laparoscopic pancreatic cyst jejunosotomy has transitioned from a loop jejunostomy to a Roux-en-Y limb cystjejunostomy for better diversion of enteral contents.[43] For this technique, four to five trocars are placed in the lower abdomen in an arc fashion to allow for intraoperative laparoscopic ultrasound, better mobilization of the Roux limb, and easier access to the lesser sac. The intraoperative ultrasound portion of the operation is critical since it allows better visualization and sample acquisition and aids in identifying the best position for a cystjejunostomy. The cyst can be approached via an opening through the transverse mesocolon just left of the middle colic vessels above the ligament of Treitz or through the gastrocolic omentum. The Roux limb is created by dividing the jejunum at least 40 cm from the ligament of Treitz, and a side-to-side jejunojejunostomy is created 50 cm distally with an additional linear stapler. The enterotomies can be closed with a continuous suture or a linear stapler. The Roux limb is then brought up to the pancreatic pseudocyst and a 3–4-cm cystjejunostomy is created with a linear stapler or continuous locking suture.

Minimally invasive techniques used in the treatment of pancreatic pseudocysts have undergone a number of

modifications. Although there is an ongoing debate about appropriate applications of laparoscopic procedures for pseudocysts, conceptually, the clinical evidence supports decreased morbidity and comparable efficacy to traditional open surgery.[32–40] More importantly, even though these new laparoscopic procedures can be reproduced and seem more feasible and practical to some surgeons, it is imperative to understand that these procedures require a very well-skilled laparoscopic and pancreatic surgeon to obtain similar outcomes.

Lateral Pancreatojejunostomy

Pseudocysts that arise in chronic pancreatitis with pancreatic duct dilatation due to strictures can be treated by lateral pancreatojejunostomy. Generally, the pancreatojejunostomy should incorporate nearly the entire length of the pancreatic duct because of extensive disease in a fibrotic gland. A short, localized pancreatojejunostomy will often result in a recurrent pseudocyst or persistent pancreatic pain following an operation. Furthermore, the length of the pancreatic duct should be cleared of stones.

When properly applied, this procedure will produce good pain relief, but increasingly, duodenal-sparing pancreatic head resections have been employed because of the excellent symptom relief.

Pancreatic Resection

Infrequently, pancreatic resection is indicated in the treatment of a pancreatic pseudocyst. Resection may be appropriate when differentiation of a pseudocyst from a potentially malignant cystic neoplasm is difficult. In addition, pseudocysts in the tail of the gland that is associated with a pancreatic duct cutoff or destruction of the left side of the pancreas may be best treated by a distal pancreatectomy. Because of irregularities of the pancreatic duct, these resections may be complicated by a troublesome pancreatic fistula. Resection to an unobstructed duct is advisable. Rarely, pancreatoduodenectomy is indicated for the treatment of a pseudocyst in the head of the pancreas. These operations should be avoided because a duodenal-sparing pancreatic head resection is a superior treatment with considerably less risk.

Duodenal-sparing Pancreatic Head Resection

Localized resection of the pancreatic head in patients with chronic pancreatitis has been shown to be an effective treatment not only for the pain associated with chronic pancreatitis but also for associated pseudocysts. It is important to note that the pancreatic head resection should be accompanied by a long pancreatic ductotomy to facilitate unimpaired drainage for the length of the pancreatic duct; this should decrease the risk of recurrent symptoms and pseudocysts. A Roux limb pancreatojejunostomy can incorporate both the head resection and pancreatic ductotomy. These procedures require extensive experience in pancreatic surgery and can be complicated by significant bleeding and, therefore, should be performed only by the most accomplished pancreatic surgeons.

Salvage Surgery

As noted earlier, percutaneous drainage of pseudocysts resulted in the need for salvage surgery in about one third of patients treated by this method.[3,44–47] Obviously, the surgical approaches to these patients are complex and varied depending on patient presentation and previous treatment. These procedures should be performed in pancreatic surgical centers with experienced personnel.

Pseudocysts Requiring Special Considerations

Not infrequently, giant pancreatic pseuodocysts or pseudocysts complicated by splenic parenchymal involvement are encountered. Giant pseudocysts are treated best with Roux-en-Y cystjejunostomy that is placed in the most dependent location of the pseudocyst.[48] This management provides adequate drainage with a decreased likelihood of undrained portions of the cyst and subsequent sepsis.

Furthermore, pseudocysts located in the pancreatic tail may cause splenic compromise by enzymes that dissect along the splenic hilum and cause digestion of the parenchyma.[49] Disruption of the spleen may be accompanied by a massive, life-threatening hemorrhage that requires emergent distal pancreatectomy and splenectomy.

Typically, these pseudocysts result from chronic pancreatitis with pancreatic duct cutoffs, and, therefore, to avoid a pancreatic stump fistula, pancreatic resection must encompass the parenchyma containing the obliterated duct. Blood loss in these challenging operations can be decreased by preoperative splenic artery embolization.

Evidence-based Treatment

The treatment strategies for pancreatic pseudocysts have evolved for the last quarter century; however, sound

evidence to support current management strategies is lacking. The majority of published works are, at best, level III evidence, and the studies often include patients with heterogeneous diagnoses. Because of a paucity of uniform definitions and incomplete pancreatic duct evaluation, even a well-performed meta-analysis would be significantly flawed. To advance evidence-based management of pancreatic pseudocysts, pancreatologists, pancreatic surgeons, and radiologists must adhere to the strict definition of a pseudocyst as an appropriate starting point to properly classify patients. Furthermore, the etiology of pancreatitis and an injury to the pancreatic duct must be delineated. This information would provide an excellent foundation for multicenter trials that would compare endoscopic management with surgical therapy. Clearly, the time to perform rigorous clinical trials has come so that we can provide patients with the most effective treatment.

Management Scheme

Because of the multitude of options available for the treatment of pseudocysts, confusion regarding the best treatment paradigm abounds. A proposed management scheme is shown in Fig. 2. Pseudocysts less than 6 cm in size rarely cause symptoms and can be managed by observation with serial cross-sectional imaging. Symptomatic pseudocysts require careful evaluation to determine the underlying cause of pancreatic inflammation. Pseudocysts arising in acute pancreatitis and not associated with extensive pancreatic necrosis may be treated by endoscopic approaches. Alternatively, pseudocysts associated with significant pancreatic necrosis or those associated with chronic pancreatitis and duct changes should be managed by cyst-enteric drainage, pancreatojejunostomy, or pancreatic resection. Patients that have pseudocysts greater than 6 cm in size but are asymptomatic present a challenging management dilemma, and no reliable evidence exists to guide treatment. In these patients with acute pancreatitis, serial imaging may demonstrate decreasing pseudocyst size over time, and close observation is reasonable. Patients with chronic pancreatitis, however, are infrequently, completely asymptomatic and, therefore, often require treatment.

Conclusion

Recent management of pancreatic pseudocysts relies on differentiating the acute from chronic pancreatitis and associated duct abnormalities. Endoscopic methods are a primary treatment for pseudocysts, and newer operative procedures are good alternatives for the treatment of chronic pancreatitis associated with pseudocysts. The application of the appropriate treatment in symptomatic patients results in excellent long-term outcomes.

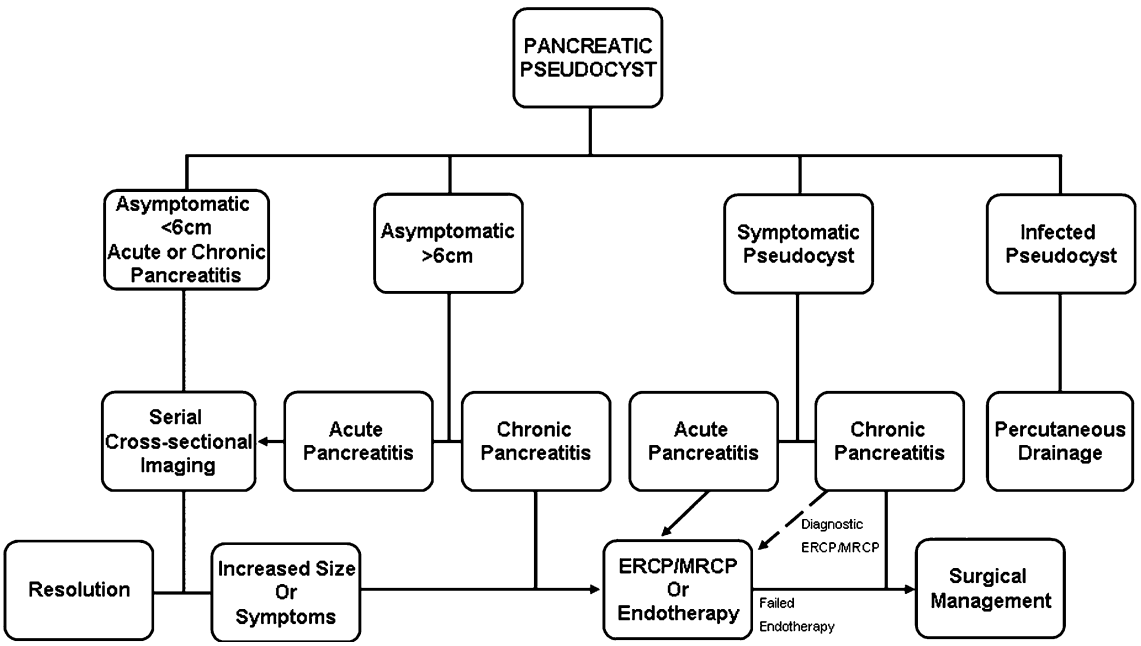

Figure 2 Management algorithm that may serve as a guideline for the treatment of pancreatic pseudocysts.

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J Gastrointest Surg (2008) 12:2240–2242
DOI 10.1007/s11605-007-0460-0

Rapunzel Syndrome Complicated with Gastric Perforation Diagnosed on Operation Table

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Received: 15 September 2007 / Accepted: 7 December 2007 / Published online: 3 January 2008

Abstract Rapunzel syndrome is a variety of trichobezoar with the main body in the stomach and the tail extending into the small or large bowel. Twenty-seven cases of Rapunzel syndrome have been reported in the literature so far. This particular case of Rapunzel syndrome was on table diagnosis in a case of gastric perforation. The bezoar was removed and the patient was given psychiatric consultation.

Keywords Bezoar · Rapunzel syndrome · Trichobezoar

Introduction

"Rapunzel" is a German fairy tale in which Rapunzel is the name of the girl who had very long silky hairs and was captivated by the witch at the top of the tower, while a Prince climbed up to rescue her by making the ladder of her long hairs. Trichobezoar in the stomach when reaches up to small or even large bowel, it is termed as Rapunzel syndrome.[1]

Case Report

A 28-year-old lady was brought to the emergency department with severe abdominal pain and distention. The lady was reluctant to speak anything, which prompted her father to reveal the facts. To begin with, it all started when the lady's husband deserted her 8 years previously because of marital discordance. Since then, she became a bit aloof of the surrounding world. Lately, she had been complaining about discomfort in her belly. Since that particular morning, she suddenly started complaining about severe pain in her abdomen, and her mother noticed that her belly was swollen.

The lady was in distress with tachycardia, hypotension, and breathlessness on examination. The abdomen was tense, tender, and distended with generalized guarding and rigidity. The erect abdominal film showed gas under both domes of the diaphragm. The unstable vital signs and free gas in the abdomen alarmed emergency laparotomy, abandoning further investigations. The peritoneum was opened with a sudden gush of air and about 3–4 l of free fluid was sucked out. A perforation of about 1 cm in diameter was found on the anterior surface of the body of the stomach. The stomach was found distended (Fig. 1) and firm in consistency even after the big perforation, suggesting some mass inside. The mass could be palpated from the gastroesophageal junction till the proximal few inches of the jejunum. On careful examination, black hairs were seen through the perforation and the diagnosis of trichobezoar was made. A vertical incision was kept over the stomach through the perforation and a hairball was dislodged and taken out (Fig. 2).

The hairball was found molded into the shape of the stomach, duodenum, and proximal part of the jejunum, and its tail extended for a further 2 ft into the small bowel (Fig. 3). The stomach was closed in two layers after excising the ulcerated area around the perforation. Patient recovered well, met the psychiatrist, and started on antidepressants.

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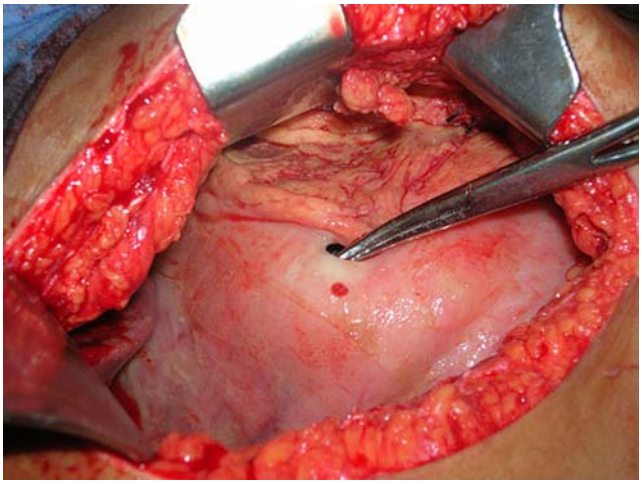

Fig. 1 Distended stomach with perforation pointed to by the hemostatic forceps.

Discussion

Bezoars are masses formed of indigestible materials found in the gastrointestinal tract. They are believed to be a physical manifestation of an underlying psychological disorder. It is postulated that hair strands too slippery to be propulsed are initially retained in the mucosal folds of the stomach and become enmeshed over a period of time. Trichobezoars are usually black from denaturation of protein by acid, glistening from retained mucus, and foul smelling from the degradation of food residue trapped within them.[2] The extension of trichobezoar into the small bowel can lead to the "Rapunzel syndrome."[3] Detached fragments of the bezoar may be detected as "satellite masses" within the small bowel and could lead to small bowel obstruction.

Trichobezoars are usually asymptomatic till they reach a critical size. Symptoms are vague abdominal pain, anorexia, vomiting, and weight loss. Hemetemesis and melena may be seen in case of gastric ulceration. Trichobezoar may cause a variety of complications, like intestinal obstruction, intussusception, and gastric perforation. Cases are reported showing gastrojejunal fistula, obstructine jaundice, and protein loosing nephropathy as complications of trichobezoar.

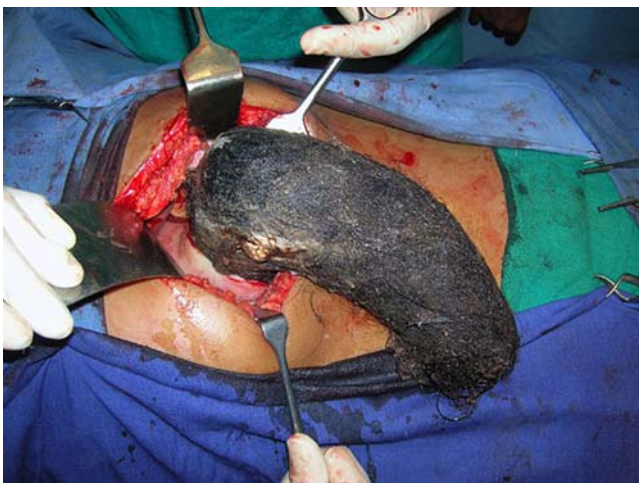

Fig. 2 Trichobezoar being pulled out of the stomach.

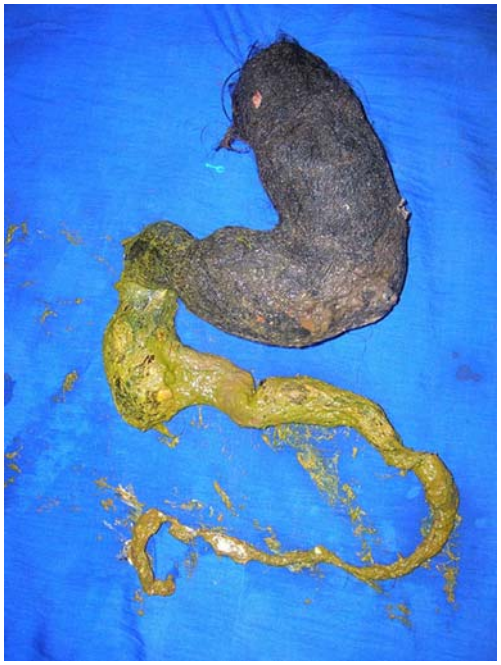

Fig. 3 Trichobezoar with extension into small bowel.

Conventional radiography may show gastric trichobezoar as mottled soft-tissue opacity in the shape of the distended stomach. Ultrasonography is the first choice of investigation and demonstrates a curvilinear bright echogenic band with posterior shadowing.[4] CT can demonstrate a large, mesh-like, intraluminal mass of lower attenuation with trapped air and concentric rings.[5]

Treatment of gastric trichobezoar is surgical. Endoscopic retrieval of gastric bezoars has been reported, but the large size of the trichobezoar makes this option impractical in most cases.[6] Extracorporeal shock wave lithotripsy and endoscopy with the use of laser ignition with miniexplosions have been suggested as alternative approaches. Laparoscopic removal of a large gastric trichobezoar is becoming a common practice nowadays but the procedure is time-consuming and tedious, and the inspection of the small intestine for small broken hairballs that can cause obstruction is not possible.[7] Recurrence of bezoars is never been reported. The trauma of operation is enough to break the habit of trichotillomania.

Conclusion

Rapunzel syndrome is a rare condition, and that complicated with gastric perforation is still rarer. Although most of the cases of bezoars are diagnosed preoperatively, in case of

complications like intestinal obstruction or perforation, one should be ready for the challenges.

Acknowledgement Written consent was taken from the patient and her father regarding the publishing of this article. Authors do not have any competing interests and none of them are funded by any external source.

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J Gastrointest Surg (2008) 12:2243–2245
DOI 10.1007/s11605-008-0468-0

Anaphylactic Shock Caused by Nonruptured Hydatid Cyst of the Liver

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Received: 1 September 2007 / Accepted: 7 January 2008 / Published online: 23 January 2008

Abstract Anaphylactic reaction is a known complication of cystic hydatid disease, a parasitic infestation caused by the larval/cyst stage of *Echinococcus granulosus* that usually happens after trauma or during interventions. Nontraumatic leakage of cyst contents into the blood circulation is an uncommon triggering factor for anaphylaxis, which is rarely reported in available literatures. We describe anaphylaxis in a 47-year-old lady who was admitted for evacuation of hydatid cyst of the liver. Unfortunately, she developed signs and symptoms of anaphylaxis in the ward while waiting for her operation. However, the condition was controlled immediately, and she was taken to the operating theater for surgery. As she had not sustained any trauma in the ward and operative exploration did not reveal any macroscopic rupture, we assumed that her problem must have been caused by nontraumatic spillage of cyst material into circulation. Although the condition is not common, one should bear in mind the possibility of such diagnosis in all patients with Eccinococcous infection who develop shock especially in areas where this infestation is endemic.

Keywords Hydatid liver cyst · Anaphylactic shock · Nonruptured

Introduction

Hydatid disease or Echinococcosis is a systemic zoonosis caused by the larval stage of the *Echinococcus* tapeworm. At present, it remains endemic to many parts of the world, most notably because of the close contact between sheep, dogs, and humans.[1–6] Humans may become intermediate hosts through exposure to a definitive host, sheep, or dog, or ingestion of contaminated water or vegetables. Hydatid disease can involve almost every organ of the body.[1,2,4–6]

Classically, an intact hydatid cyst is classified as simple or typical cyst. On the other hand, a perforated cyst, with or without superinfection, is described as complicated or atypical cyst, if it had ruptured into the neighboring cavity, either spontaneously or iatrogenically.[7] Anaphylactic shock is a rare complication of hydatid cyst, which usually occurs after trauma. Familiarity with the atypical clinical presentation of Echinococcosis is very important to prevent both misdiagnosis and improper therapeutic interventions in these cases.[1]

We present a patient with hydatid cyst of the liver who developed an anaphylactic shock without known abdominal trauma.

Case Report

A 46-year-old Iranian woman was admitted to the surgical department with diagnosis of two very large hydatid cysts of the liver (Fig. 1). Twenty-four hours after admission, she

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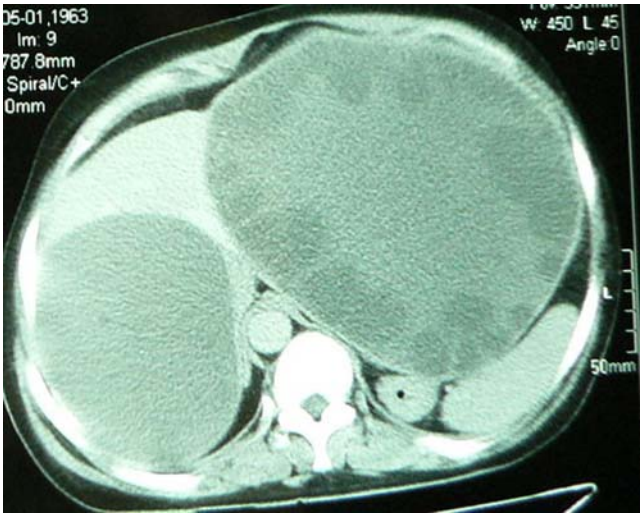

Figure 1 Abdominal CT scan of the liver showing two intact large hydatid cysts with no intraperitoneal fluid.

suddenly developed pruritus, dyspnea, cough, vomiting, and dizziness associated with generalized urticaria, wheeze, and cyanotic lips. Her blood pressure dropped to 85/55 mmHg and pulse rate increased to 133/min. Hydration, hydrocortisone, and antihistamines were used to treat the possible anaphylactic reaction/shock. At the operating theater, two large intact hydatid cysts (Fig. 2) were found in the right and left lobes of the liver with no free fluid in the peritoneal cavity. After closed evacuation, cysts were unroofed and marsupialized with running interlocking sutures. The small visible bile ducts were tied off and homeostasis was achieved. The abdominal wall was closed after leaving a closed suction drain in place. The patient had no postoperative complication but bile leak through the drain, which stopped gradually in 2 months time. No recurrence was detected after 12 months follow-up.

Discussion

Anaphylactic reaction to hydatid cyst usually occurs after microscopic or macroscopic rupture of cyst and leakage of contents into the peritoneum or blood circulation. The hydatid cyst of the liver has three layers: the outer layer is a dense fibrous tissue; the middle laminated membrane is an acellular layer, which allows the passage of nutrients; and the inner germinal layer consists the scolices, which is the larval stage of the parasite.[7] The outer layer is called pericyst, and the combination of middle laminated membrane and the germinal layer are known as the endocyst.[8] Hydatid cyst has a high pressure inside and contains clear or pale yellow fluid with strong antigenic effects.[8] Rupture into the abdominal cavity is a rare but serious complication, which may occur spontaneously or after trauma.[9,10]

In the presence of any rupture or leakage, an allergic reaction is evoked because of the spillage of the allergic contents of the cyst into the surrounding tissues.[7,11] The response can be from a mild hypersensitivity reaction to a fatal anaphylactic shock. In this patient, the cystic walls were intact, and we believe that high intracystic pressure must have been the cause of leakage of cystic fluid into the circulation. After reviewing literatures, we could hardly find few reports of anaphylactic reaction/shock to hydatid cyst with no apparent macroscopic rupture.[12] Although this condition is not common, it should be considered as one of the differentials in every patient with hydatid disease who develops shock state with no other obvious causes.[12,13]

Conclusion

Rupture or leakage of echinococcal cysts are not predictable and can happen with no trauma or intervention. Anaphylactic reaction in a patient from an area where *Echinococcus* is endemic might be a result of undiagnosed hydatid cyst, which should be evacuated after early resuscitation. Increased awareness of this possibility in these areas is encouraged.

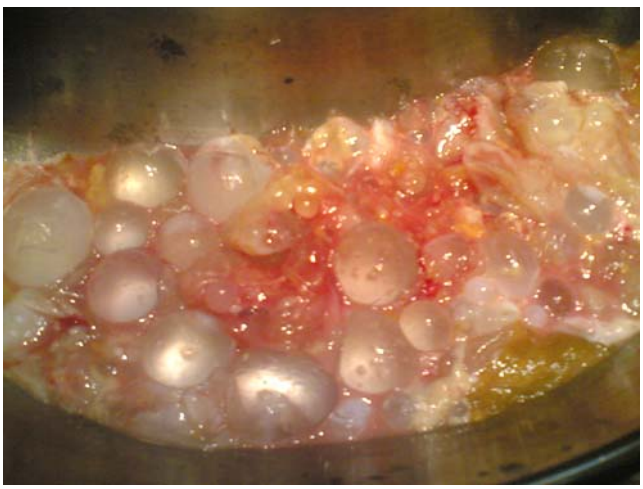

Figure 2 Operative photograph showing evacuated daughter cysts of the hydatid cysts.

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J Gastrointest Surg (2008) 12:2246–2247
DOI 10.1007/s11605-008-0608-6

The Azygos Vein: to Resect or Not?

Judith Boone · Richard van Hillegersberg

Received: 5 May 2008 / Accepted: 9 May 2008 / Published online: 2 August 2008

Dear Editor,

With great interest we read the article by Schröder et al. to be published in a forthcoming issue of the Journal of Gastrointestinal Surgery in which they investigated the potential value of resecting the azygos vein in transthoracic esophagectomy for esophageal cancer.[1]

During (robot-assisted) thoracoscopic esophagectomy, the trunk of the azygos vein is often preserved as the scopic ligation of the numerous intercostal veins is technically difficult and time-consuming.[2–6] One may postulate that this may negatively affect the extent of lymph node harvesting or the circumferential radical (R0) resection rate.

Schröder et al. have, therefore, performed a prospective evaluation on the amount of lymph nodes surrounding the azygos vein in 92 patients with esophageal cancer having undergone open transthoracic esophagectomy with two-field lymphadenectomy.[1] Lymph nodes near the azygos vein were identified in 65% of patients and metastases in these lymph nodes were found in 8%. They, therefore, conclude that the dissection of the azygos vein should not be abandoned, irrespective of the surgical approach.

A comment should be made on the design of the study. As clearly shown in Figure 2 of their article, they dissected the azygos vein with the surrounding tissues sharply from the esophagus, which is not representative for (robot-assisted) thoracoscopic esophagectomy. In (robot-assisted) thoracoscopic esophagectomy, subsequent to the ligation of the azygos arch, the mediastinal dissection of the esophagus and surrounding tissues is performed sharply along the azygos trunk. In this way, the fatty tissue in between the esophagus and the azygos vein (including the lymph nodes of stations 108 and 110) as well as the thoracic duct are included in the esophageal resected specimen and are not left in situ when the trunk of the azygos vein is preserved.[2] The number of lymph nodes that will be left in situ with (robot-assisted) thoracoscopic esophagectomy will, therefore, be much less than stated in this article. Indeed, in our recently published cadaveric study in which we investigated an identical research question, a mean amount of only 0.67 lymph nodes were identified around the azygos vein using the thoracoscopic dissection method.[7] Using this approach, in 60% of cadavers, no lymph nodes near the azygos vein were detected at all. With regard to the possible effect of azygos vein preservation on the radical resection rate, we can refer to our first report on 21 esophageal cancer patients having undergone robot-assisted thoracoscopic esophagectomy. The R0 resection rate of 76% in that series is similar to that of open transthoracic esophagectomy.[2,8] In our opinion, it is, therefore, justified to preserve the azygos trunk during (minimally invasive) transthoracic esophagectomy.

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J Gastrointest Surg (2008) 12:2248
DOI 10.1007/s11605-008-0612-x

Response—The Resection of the Azygos Vein—Necessary or Redundant Extension of Transthoracic Esophagectomy

W. Schroeder · A. H. Hoelscher

Received: 30 June 2008 / Accepted: 8 July 2008 / Published online: 11 September 2008

Dear Editor,

The reply to our article demonstrates the general interest of this topic coming up with the new surgical technique of minimally invasive esophagectomy.

From the authors point of view, it is important to emphasize that this is a morphological study predominantly focusing on the number of harvested lymph nodes associated with azygos vein resection. The study does not investigate a possible prognostic benefit related to a more extended mediastinal lymphadenectomy.

We agree with the Dutch colleagues that the majority of resected lymph nodes are located between the tubular esophagus and the azygos vein. Consequently, a sharp dissection of the connective tissue along the azygos vein without resection should result in the same number of mediastinal lymph nodes harvested. However, using this (robot-assisted) technique, the number of resected lymph nodes is far less compared to our technique of transthoracic en-bloc esophagectomy with a complete azygos vein resection. Assuming that the pathological work-up of the specimen is similar, this difference can only be explained by the extension of lymphadenectomy. In fact, a complete dissection of the connective tissue from the descending aorta is easier to perform from the lateral aspect of the azygos vein. Irrespective with this discussion, there is no doubt that many esophageal surgeons using the minimally invasive access just dissect along the tubular esophagus without incorporating the fatty tissue between esophagus and azygos vein. As demonstrated in this study, this approach will definitely reduce the number of harvested lymph nodes and possibly the survival benefit.

The resection of the primary tumor (R0 vs. R1) is not affected by the question of azygos vein resection.

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J Gastrointest Surg (2008) 12:2249–2250
DOI 10.1007/s11605-008-0657-x

Letter to the Editor—Early ERCP for Gallstone Pancreatitis: For Whom and When?

Behrns KE, Ashley WS, Hunter JG, Carr-Locke DC, J Gastroenterol Surg 2008;12:629–633

Juan Miguel Acosta

Received: 22 July 2008 / Accepted: 5 August 2008 / Published online: 23 August 2008

I read with interest the article recently published in the *Journal of Gastrointestinal Surgery* in which Behrns et al. reported the result of an evidence-based review of the outcomes of early endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis. The study adds to the slow-growing knowledge of evidence supporting advantages and disadvantages from the use of this procedure, but not much. The study does not provide a careful evidence-based analysis of the data in relation to duration of ampullary obstruction provided in the trials analyzed. In fact, excepting the time of ERCP calculated from admission and, more recently, from the onset of symptoms, no other data have been reported in most publications about this point. Apparently, there is no doubt at present that the time of the onset of symptoms is the time of stone impaction, and consequently, it is also the time of the onset of obstruction. Likewise, the time of ERCP + endoscopic sphincterotomy (ES) is considered the time of the end of obstruction. However, the fact that 80–90% of the patients with obstructive gallstone pancreatitis pass the stone spontaneously within 48 h from the onset of symptoms makes necessary to find other indicators than ERCP since it is not completely innocuous, and moreover, it is irrelevant once the stone has passed. Our study—one of the studies analyzed by Behrns et al.—reports a non-invasive and accurate method for measuring the duration of ampullary obstruction in that important group of patients who disobstructs spontaneously. It also permits to evaluate the relationship between patient outcome and duration of obstruction regardless of whether the last is due to ES or to the natural history of the disease. The authors stated that our method can be "subjective and open to interpretation." As the authors noted, our diagnostic test consists of three variables: severe unremitting epigastric pain, bile-free gastric aspirate, and persistent or increasing serum bilirubin level serially determined every 6 h from admission to normalization. Excepting pain, the other two variables are very objective and permit to omit ERCP + ES when they are unnecessary. It has been employed for our group for many years, and its accuracy has been validated in a previous publication (Acosta et al., *Am J Gastroenterol* 2000;95:122–127). The following unpublished data is part of our study and may illustrate on the calculation used to define the accuracy of our method.

Accuracy of the Diagnostic Test Used for Monitoring Ampullary Obstruction in 61 Patients with Acute Biliary Pancreatitis[1]

Accuracy factor	Ampullary obstruction monitoring (n=61)
Sensitivity	1.0
Specificity	0.92
Positive predictive value	0.88
Negative predictive value	1.0

Clinical picture consistent with acute gallstone pancreatitis, particularly severe and continuous epigastric pain, bile-free gastric aspirate, and persistent or increasing elevated serum bilirubin level determined every 6 h from admission to normalization.

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[1] Acosta et al., *Ann Surg* 2006;243:33–40

Definitions accuracy factors:

True (+): Patients in whom a positive test for ampullary obstruction was confirmed by endoscopic retrograde cholagiopancreatography (ERCP; n=15); 11 of them showed a stone impacted at the ampulla; three showed edema of the papilla, and the remained patient, sludge. All the 15 patients underwent ES.

False (+): Patients in whom a positive test for obstruction was not confirmed by ERCP (n=2). These patients showed papillary edema without obstruction and ES was not performed.

True (-): Patients in whom a negative test for ampullary obstruction was confirmed by a subsequent favorable clinical and laboratory course plus operative findings at elective cholecystectomy at first admission (n=44) including intraoperative cholangiography (IOC) in 14 and urgent (n=2) or elective (n=6) ERCP.

False (–): Patients with a negative test in whom disobstruction was not confirmed by clinical, laboratory, imaging, or operative methods (n=0).

Calculation used in the data[2]

	Ampulary Obstruction Present	*Ampulary Obstruction absent*	**Total Tests (+) + (–)**
Positive Test	TRUE + 15	FALSE + 2	17 { (TRUE +) + (FALSE +)
Negative Test	FALSE – 0	TRUE – 44	44 { (FALSE –) + (TRUE –)
Total presence and absence of the condition	(TRUE +) + (FALSE –) } 15	(FALSE +) + (TRUE –) } 46	61

Sensitivity = TP/(TP + FN) = 15/15 + 0 = 1.0
Specificity = TN/(TN + FP) = 44/44 + 2 = 0.96
Positive predicted value = TP/(TP + FP) = 15/15 + 2 = 0.88
Negative predicted value= TN/(TN + FN) = 44/44 + 0 = 1.0

[2] Anderson BJ, Deyo RA, 2nd ed. Philadelphia: Lippincott-Raven Publishers;1997:305-317.

J Gastrointest Surg (2008) 12:2251–2252
DOI 10.1007/s11605-008-0656-y

RE Early ERCP for Gallstone Pancreatitis: For Whom and When?

Behrns KE, Ashley SW, Hunter JG, Carr-Locke DC.
***J Gastrointest Surg* 2008;12:629–633 Reply to Letter to the Editor**

Kevin E. Behrns · Stanley W. Ashley · John G. Hunter · David Carr-Locke

Received: 28 July 2008 / Accepted: 5 August 2008 / Published online: 3 September 2008

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July 28, 2008

We read with interest Dr. Acosta's letter to the editor regarding the use of endoscopic retrograde cholangiopancreatography (ERCP) in patients with gallstone pancreatitis. Certainly, Dr. Acosta and colleagues have made several, seminal contributions to the literature of gallstone pancreatitis, and his valuable contributions have advanced our understanding of the pathophysiology and treatment of this disease.

In our evidence-based review,[1] we examined the body of literature supporting or detracting from the use of ERCP in gallstone pancreatitis with particular emphasis on whom the procedure should be performed, and if so, when it should be performed. We cited Dr. Acosta's work[2] that suggested that patients with persistent ampullary obstruction (>48 h) in the setting of gallstone pancreatitis undergo ERCP with sphincterotomy. In this review, we challenged the three criteria of persistent ampullary obstruction. These criteria are severe, unremitting epigastric pain, bile-free gastric aspirate, and persistent or increasing serum bilirubin concentrations. We suggested that these criteria are subject to interpretation and may be capricious.

In his letter, Dr. Acosta agrees that the interpretation of pain is subjective. However, we maintain that the determination of bile-free gastric aspirate every 6 h may be quite inconsistent. First, the data are dependent on prompt patient presentation to the treating institution since the three predictive factors were measured within 48 h of symptom onset. Few patients are available within that time frame, and, in fact, in Dr. Acosta's study, two thirds of the patients were excluded, likely because many of these patients did not meet the time criteria for patient presentation to the treating institution. In addition, determination of bile-free gastric aspirate requires nasogastric intubation, which is not universally applied in this group of patients. In fact, only 10% of patients in Dr. Acosta's study had severe pancreatitis, and thus, the vast majority of patients probably did not need a nasogastric tube for therapeutic purposes. Lastly, although serum bilirubin concentrations are objective, what amount of increase or decrease in a bilirbuin concentration is deemed significant?

Finally, it is very unlikely that these three predictive factors are all concordant simultaneously. If, indeed, this is the case, then from the statistical analysis point of view, how are these discrepancies reconciled? Even though Dr. Acosta references previous work[3] that validates the use of these predictive factors, the data from this study indicate that the positive predictive value for ampullary

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obstruction was 0.61. Thus, a little more than half of the patients are accurately diagnosed with ampullary obstruction. If ampullary obstruction cannot be reliably determined, then disobstruction must be equally unreliable.

We appreciate Dr. Acosta's insight and comments but steadfastly maintain our conclusion that ERCP should not be routinely performed in patients with mild gallstone-induced pancreatitis, and that for select patients with severe pancreatitis or documented biliary obstruction, ERCP may be therapeutic.

Thank you for the opportunity to respond to this letter.

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