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SSAT OTHER

Report of the 2007 Education Committee Panel on Simulation in Alimentary Tract Surgery

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Abstract At the 2007 Digestive Diseases Week, the Education Committee of the Society for Surgery of the Alimentary Tract sponsored a symposium entitled "Simulation in Gastrointestinal Surgery." Four panelists presented perspectives on the role of simulation in education and training of medical students and residents in operations of Gastrointestinal Surgery in the gastrointestinal surgeon's practice, in the certification of centers for training and maintenance of skills, and in the credentialing of surgeons in new procedures. The consensus of the panel is that over the next several years, simulation will play an expanding role in all of these spheres of the GI surgeon's activities.

Keywords Simulation · Procedure-based specialists · Gastrointestinal surgery

Introduction

For many years, an increasing amount of attention has been focused on the environments in which students and residents learn to perform well-established surgical procedures. More recently, the discussion has turned to the practicing surgeon who must maintain proficiency in acquired skills and also develop new ones that require use of complex tools and technologies. The need for procedure-based specialists to provide ongoing assurance of the safety and competence with different procedures has been likened—with some qualification—to the requirements that airline pilots meet to get a plane safely off the ground and back down again. The airline metaphor has been embraced in the surgical community at large,[1,2] in the military,[3] and in lay press,[4,5] and with it, the idea that surgeons can learn a lot from simulation.

In this symposium, organized by the Education Committee of the SSAT, four panelists presented perspectives on the role of simulation in education and training of medical students and residents in operations of Gastrointestinal Surgery, in the gastrointestinal surgeon's practice, in the certification of centers for training and maintenance of skills, and in the credentialing of surgeons in new procedures. Their perspectives are published in the four articles that follow this introduction.

Perspectives

Dr. Carlos Pellegrini, along with his co-authors Drs. Johnson and Sachdeva, have focused on the need for Centers of Simulation Training that meet high standards for quality of their educational programs. Their perspective emphasizes that organizations such as the American College of Surgeons should provide leadership in accrediting Programs of Education related to simulation and training in new technologies, much as the College has taken on an accrediting role for Programs of Cancer Management and Trauma/Burn Management. The argument is that in the long run, such processes of accreditation will improve safety and outcomes for patients and decrease liability for participating surgeons and health care institutions. Unstated, but not far

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from the surface of their discussion, is the implied danger of the American College of Surgeons (ACS) not taking the lead in accreditation, which raises the specter of a proliferation of pre-Flexnerian, for-profit proprietary programs that would grant certificates of training without valid methods for assessing the proficiency of the learners.

Dr. Gerald Fried has described the process by which the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) developed an approach to teaching fundamental manual skills in laparoscopic surgery. An important adjunct to the program was the development of a testing arm, one that ensures that the learner can demonstrate the acquisition of the basic skill. In the panel's discussion, it was noted that in some areas of the country, insurers have already taken notice of the program and are offering discounts in premiums to individual surgeons who demonstrate proficiency in basic skills. The presentation and the discussion underscored a promising advance in relationships between payers and providers: that the stick of "pay for performance" might be mollified at least partially by a carrot of "compensation for capability."

With his co-author Dr Dunnington, Dr. Daniel Scott has reported on the initiatives in Residency Education taken by the Association of Program Directors in Surgery, in conjunction with the American College of Surgeons. Dr. Scott summarizes the results of recent surveys of residency training programs regarding availability and usage of skills labs. Remarkably, only about half had such labs, and of these, perhaps two thirds have documented curricula. In response, the APDS and the ACS have sponsored a collaboration among educators throughout North America, the Surgical Skills Curriculum Task Force, challenging them to identify the best training practices and to devise a National Skills Curriculum based on simulation approaches that are validated but also affordable to most programs. The description of the approach is well worth the consideration of senior surgeons who sure wonder how, in the era of the 80-h work week for trainees, to teach students and younger residents the "fundamentals" and also how to recognize and correct unsafe or inefficient habits in the more experienced trainees.

Lastly, Dr. Daniel Jones provided a perspective on the use of an entire "mock operating room" for training of young surgeons and credentialing of all surgeons. Dr. Jones' presentation focused on integration of the entire experience in the operating room as well as on the problem of teaching the learner how to see the field and understand the goals of the operation. Also described is the manikin patient that can bleed or go into shock and scripted OR personnel who will create errors or near-miss disturbances at the will of an unseen organizer. The goal is to condition the unsuspecting learner (surgeon) to reinforce individual and team conduct that solve unexpected problems, improve communication, and restore equanimity quickly. An additional goal is to root out behaviors that exacerbate poor performance and increase anxiety. With the recent recognition that human factors contribute significantly to the propagation of management errors and communication breakdowns in the OR,[6,7] Dr. Jones' presentation highlights the need to focus on performance of the entire team and not just the development of virtuoso surgeons.

Summary

In the context of alimentary tract surgery, the benefits of simulation for trainees and practicing surgeons are becoming increasingly clear. The presentations at the 2007 SSAT Education Committee Program emphasized evolving opportunities for GI surgeons to utilize simulation strategies for teaching basic skills in open and laparoscopic surgery and for integration of skills and behaviors that lead to best practices in the operating rooms and best outcomes for patients. Also highlighted was the collaboration between different organizations such as the American College of Surgeons (ACS), the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), and the Association of Program Directors in Surgery (APDS). The message of the panel discussion is that organizations such as the SSAT should embrace these initiatives and disseminate information about them to its membership.

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The Critical Role of Accreditation in Establishing the ACS Education Institutes to Advance Patient Safety Through Simulation

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Abstract This paper reviews the rationale for the development of an accreditation program for Educational Institutes by the American College of Surgeons. It discusses the reasons why such accreditation program is beneficial to the institutes themselves as well as to the organizations that sponsor the institute. It analyzes the evolution of the accreditation program since its inception, and it provides advice as to how to start the accreditation process.

Keywords Accreditation · ACS education institutes · Simulation

Advancing patient safety is part of the core mission of the American College of Surgeons (ACS). Since the very inception of the ACS, its leadership felt that one of the ways the ACS was going to address this core value was through the process of education. Over the years, the delivery of education has been accomplished primarily through the activities of its Clinical Congress and through its participation in a number of postgraduate courses. As simulation became an integral part of surgical education, not only as a unique tool to facilitate the acquisition of technical skills but a part of the armamentarium available to train teams of health professionals, enhance communication skills, and address several other competencies of modern surgeons, the ACS sought to determine additional ways in which it could contribute to the advancement of this relatively new field. After extensive discussions that took place under the aegis of the ACS Division of Education, the decision was made to accredit facilities that focus on surgical education and address surgical knowledge and skills. The leadership of the ACS felt that through this process, it would be in a position to set standards that fit within the most modern educational principles while using a method (accreditation) with which ACS had substantial experience. This article describes the essence and benefits of accreditation as the foundation on which the ACS Accreditation Program for Educational Institutes is built.

Value of Accreditation

An accreditation system is a process an organization goes through to demonstrate its ability to meet established standards and criteria to achieve a specific status from a recognized governing body.

Faced with the opportunity to seek accreditation, individuals within organizations frequently ask themselves why. Knowing that to achieve accreditation the organization will have to commit certain resources, it is important to understand the value of accreditation to the organization. To those who work within the confines of health care, accreditation is viewed as the process by which standards are established to improve quality care.[1] This is usually achieved by assuring adequacy of training, development of standard operating procedures and other activities that

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enhance safety, promote efficiency and assure timely completion of all related tasks, which in the end will benefit patients. Oftentimes, organizations use accreditation to inform stakeholders they are committed to quality, through their ability to demonstrate their compliance with a particular set of standards.[2] For the past 30 years, the public has come to expect, at least within the health care field, that having high quality is synonymous with having technical excellence.[1] With this as the perception, medical education has been the vehicle by which physicians and surgeons achieve technical excellence through their participation in certified medical education activities provided by institutions that are accredited. These organizations have demonstrated their ability to meet accreditation standards of organizations such as Accreditation Council for Continuing Medical Education and Accreditation Council for Graduate Medical Education.[3,4] By becoming accredited, organizations are demonstrating they are committed to providing good education all of the time. An unintended impact of accreditation for many organizations is the commitment to self-monitoring; ensuring standards are always met, and ensuring the quality of their programs.[5]

Benefits of Accreditation

So how then do the values of an accreditation program turn into actual identifiable benefits that the organizations can measure? One benefit is the generation of new business.[2] Oftentimes, consumers look for the "Good Housekeeping Seal of Approval" before purchasing a product or service. The same could be true in health care. For example, if there are two health care organizations in town, and one is accredited and the other is not, patients may be drawn to the accredited organization because they have demonstrated they have met certain standards.

In the health care industry, having an accreditation status may result in lower premiums,[2] due to an organization's decision to go through an accreditation process. This decision demonstrates the organization's commitment to quality and standards. An often subtle but important benefit of pursuing accreditation is the empowerment of those in charge of the unit seeking accreditation (i.e., the Educational Institute in our case) to seek additional resources from a variety of internal sources to comply with accreditation standards. The decision on the part of the larger organization to have one of its units or parts accredited implies a willingness to provide the necessary resources to meet certain standards. Thus, acquisition of new space, support for additional personnel, and equipment are all facilitated internally (in a way they are easier to "justify") as they respond to an external fixed standard.

In addition, the accreditation process provides a unique opportunity for self-examination, setting of new directions, development of new strategic plans and integration of individuals with similar interests. Our experience indicates that, without realizing it, organizations that are in the process of accreditation advance substantially in the understanding of their own values and attitudes. This process, thus, has value in and of itself independent of the success of the accreditation request. For example, nursing homes accredited through JCAHO demonstrated fewer deficiencies than nursing homes not accredited.[5] The data suggest accredited organizations are continually working towards meeting standards and improving quality.

Finally, another benefit of accreditation is the potential for collaboration among organizations that have been accredited—and thus share the same threshold standards, ideas, and beliefs. This collaboration may promote standardization of performance measures, the reduction of duplicative processes, and the sharing of data.[1]

The ACS Program for Accreditation of Education Institutes

Since 1917, the American College of Surgeons has used standards as a measurement tool to accredit organizations to enhance patient care.[6] In more modern times, the College has continued the practice of utilizing standards to accredit organizations within specific health care areas. Two examples that are widely known and respected are the trauma and cancer accreditation programs. In 2003, the ACS Division of Education proposed to the ACS Board of Regents a concept that involved the creation of standards reflecting the most modern educational principles and to use those standards to accredit education institutes that comply with them.[6] The Board of Regents gave its enthusiastic approval, and an Ad Hoc Committee started the development of standards for the program to accredit education institutes. This Committee wanted to ensure that whether a surgeon was taking a course in Seattle, WA or Columbus, OH, the important aspects of the education process would be the same. Additionally, the committee believed it would be valuable to create uniformity with respect to the documents and forms used in the program. Standardization of requirements, processes, training, and how decisions are made and communicated to all involved are vital and key to the success of any accreditation program. The accreditation model was developed, and surveyors were trained. Two review committees were appointed by the ACS Board of Regents and were given the authority to accredit education institutes using the established standards and criteria. The accreditation model

assures consistency in decisions through the use of standardized criteria and processes.

The ACS accreditation program provides assurance to the health care community and the public that an accredited education institute has met the rigorous standards of the program and provides a venue for high-quality surgical education and assessment for surgeons, surgical residents, and members of the surgical team. For the accredited Education Institutes themselves, there are multiple benefits including the possibility to become a member of a network of Education Institutes that can share data and information, create innovative surgical curricula and participate in multi-institutional research.

As the process has evolved, the ACS-accredited Education Institutes are now leading the way in the provision of surgical education in its broadest scope (i.e., beyond pure psychomotor skill development) to medical students, residents in surgery and practicing physicians who wish to acquire new skills or who wish to improve previously acquired skills. Research in surgical education, creation of new tools for learning and the ability to interact in a broad network puts these institutes at the leadership of surgical education.

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FLS Assessment of Competency Using Simulated Laparoscopic Tasks

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Abstract Fundamentals of Laparoscopic Surgery (FLS) is a program of SAGES and the American College of Surgeons designed to teach and evaluate the knowledge, judgment, and skills fundamental to laparoscopic surgery, independent of the surgical specialty. It has undergone rigorous evaluation to ensure that the evaluation component meets appropriate standards to ensure the reliability and validity of the test. The manual skills component is based on the McGill Inanimate System for Training and Evaluation of Laparoscopic Skills (MISTELS) program. This component has been shown to meet standards for reliability (interrater, test–retest, and internal consistency) required for a high-stakes examination. Content, face, construct, and criterion validity have also been established through a series of experimental studies. FLS presents a comprehensive learning package that is inexpensive and of proven value for teaching minimally invasive surgery. Its unique contribution is the included validated assessment to ensure that those taking the program have demonstrated the requisite knowledge and skills fundamental to performing laparoscopic surgery.

Keywords Laparoscopy · Minimally invasive surgery · Simulation · Education

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The fundamentals of laparoscopic surgery (FLS) was developed by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) with the goals of providing standardized fundamental information about laparoscopic surgery, and teaching a set of technical skill exercises that, once mastered, correlate with improved clinical performance in laparoscopic operations. This program was directed at the level of the practicing surgeon and senior surgical residents. It is not procedure-specific and thus could be used by not only general surgeons, but also by urologists, gynecologists, or thoracic surgeons practicing minimally invasive surgery.

In addition to its educational objectives, FLS was developed with the principle that learning should be verified by an associated assessment arm, produced to meet the standards of a high-stakes examination. This is to ensure the learner had acquired the requisite knowledge, judgment and skills fundamental to laparoscopic surgery. This would establish minimum standards of cognitive and technical skills.

This paper will focus on the manual skills component of the FLS program, recognizing that FLS is an integrated curriculum of knowledge and skills, and its authors are strongly committed to teaching and evaluating laparoscopic cognitive and technical skills together.

Description of the FLS Manual Skills Component

The manual skills component of FLS was designed to teach and evaluate the fundamental skill set specific to minimally invasive surgery (MIS). After review of videotapes of MIS procedures, a group of experienced surgeons listed fundamental differences between MIS and open surgery (monocular vision/limited depth perception, magnification, fixed access through trocar/decreased degrees of freedom, fulcrum effect, long instruments that amplify tremor and provide decreased tactile feedback).

These then formed the basis for exercises modeled in a physical (endotrainer box) simulator. The optical system presents a monocular view of a series of objects that must be manipulated to perform five tasks of increasing complexity (peg transfer, cutting/dissecting, placement of a ligating loop to secure a tubular structure, and suturing with either intracorporeal or extracorporeal knot tying). The camera view and trocar positions are standardized, and actual commercially available laparoscopic instruments are used. Each task is scored using measures of efficiency (time) and precision, with penalties assigned for errors. A trained proctor observes the learner and scores each task. Depending on the skill of the surgeon, it takes 45–60 min to complete the exercises. These are based on the MISTELS program described previously.[1] The FLS technical skills component was designed to be robust, portable, flexible, and inexpensive.

Scott et al.[2] have developed a curriculum specifically designed to teach the FLS skills to trainees. They have shown that was planned distributed practice, even novice surgeons could achieve a passing score within a reasonable time frame.

A series of studies were performed to evaluate the FLS metrics for reliability, validity, feasibility to administer, and to determine an appropriate passing score for the test.

Validation of FLS Metrics

Reliability FLS metrics were tested for reliability to ensure consistency between raters, between repeated testing of the same individual, and between the five test items.[3] Interrater reliability was 0.998 (0.985–1.00) and test–retest reliability was 0.892 (0.665–0.968), each represented as mean with 95% confidence intervals, as measured using the intraclass correlation coefficient. Internal consistency (Cronbach's alpha) was 0.86, and internal consistency could not be improved with the deletion of any task. Each task correlated highly with the total score (correlations=0.62–0.81). Generally a reliability of >0.80 is desired for high stakes testing but is often difficult to achieve for evaluation of manual skills.

Validity The manual skills program was assessed for validity in several ways. Content validity and face validity were determined by questioning a group of experts in MIS by asking "Does the test (simulator) evaluate the appropriate (specific) content and breadth of content?" and "On the face of it, do the metrics seem credible measures of the construct in question?" (face validity). Using a global rating scale, the panelists attested to the credibility and content of the metrics.[4,5]

Construct validity was assessed by demonstrating differences between groups expected to perform at different levels. When stratified by level of training or experience, or by self-assessment of competence, the FLS metrics were able to determine expected differences.[1,5] Samples were drawn of 215 surgeons from diverse backgrounds and skill levels, and from 5 countries.

Criterion validity can be tested through demonstration of concurrent validity or predictive validity. These were established using a number of other surrogate measures of technical skill-in-training evaluation reports of residents in training, performance doing structured tasks in live animals, and assessment of intraoperative skill while performing a laparoscopic cholecystectomy using a reliable and validated global rating scale.[1,6] These studies showed the FLS program to meet very high standards for reliability. Furthermore, McCluney et al.[7] have shown that FLS score is predictive of intraoperative performance.

Use of FLS Scores for Summary Evaluation

Fraser et al.[8] developed receiver operating curves to determine the FLS score that differentiated between "competent" and "noncompetent" laparoscopic surgeons with the highest sensitivity and specificity. Using this methodology, they found that a FLS score could be identified to separate these groups with sensitivity and specificity for this test that both exceeded 0.80. This score was used as the basis for establishing a passing score for the manual skills component of the FLS test. Using this as a cut-off score, 82% of competent MIS surgeons would pass, and <20% of noncompetent surgeons would pass.

Summary

The FLS manual skills program is based on an inexpensive, portable, and practical physical simulator designed to train and assess MIS skills. Using it to practice skills results in improved laparoscopic skill as seen in the operating room. FLS measurements are highly reliable and valid measures of laparoscopic skill.

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SSAT OTHER

The New ACS/APDS Skills Curriculum: Moving the Learning Curve Out of the Operating Room

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Abstract Surgical education has dramatically changed in response to numerous constraints placed on residency programs, but a substantial gap in uniform practices exist, especially in the area of skills laboratory availability and usage. Simulation-based training has gained significant momentum and will be a requirement for residencies in the near future. In response, the American College of Surgeons and the Association of Program Directors in Surgery have formed a Surgical Skills Curriculum Task Force with the aim of establishing a National Skills Curriculum. The first of three phases will undergo implementation in 2007, with subsequent phases scheduled for launch in 2008. The curriculum has been carefully structured and designed by content experts to enhance resident training through reproducible simulations, with verification of proficiency before operative experience. Free-of-charge distribution is planned through a web-based platform, and widespread adoption is encouraged. In the future, these simulation-based strategies may be useful in assuring the competency of practicing surgeons and for credentialing purposes.

Keywords Surgical education · ACS/APDS skills curriculum · Skills laboratories · Simulation · Proficiency-based training · Competency

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Introduction

Since the apprenticeship model for residency training was introduced by William Halsted over a century ago, surgical education has evolved immensely. These changes have been to a large extent the direct result of the ongoing introduction of numerous constraints.[1] Program directors now face the substantial hurdles training in the modern healthcare environment. For instance, in 2003, the Residency Review Committee (RRC) introduced the 80-h workweek, which has likely had a positive impact on lifestyle issues and the recruitment of medical students into surgical careers, but may also have serious connotations regarding the manner in which training is conducted.[2,3] A considerable burden is now on program directors to ensure that adequate case volumes and educational objectives are achieved such that competent surgeons are graduated.[4] Accordingly, resident training must now be more efficient, relying more on the principles of adult education rather than on service.

Similarly, due to practice patterns and limitations in operative time, adequate case volumes, as specified by the Accreditation Council on Graduate Medical Education (ACGME), may be difficult to achieve.[5] This is especially

true for many advanced gastrointestinal, laparoscopic, and endoscopic procedures, and minimum case numbers in several of these areas have recently been increased.[6] Financial constraints have further limited opportunities for teaching in the operating room.[7] Additionally, the public has gained a heightened awareness of the occurrence of medical errors, and patient safety concerns have placed resident training, as well as the training of practicing surgeons in new procedures, squarely in the limelight.[1,4,8]As technology continues to evolve, issues concerning the safe adoption of new procedures into clinical practice will undoubtedly remain a prominent topic.

In the midst of many of these issues, several national organizations have worked diligently to assure the competency of surgeons. For residents, the ACGME introduced the six core competencies (Table 1), which are designed to comprehensively define training objectives.[5] For practicing surgeons, the American Board of Surgery (ABS) adopted these same competencies and instituted four components for Maintenance of Certification, including professional standing, lifelong learning, cognitive expertise, and evaluation of performance in practice. While many aspects of the ACGME and ABS guidelines can be verified using conventional methods, it is clear that new strategies for assuring competency are needed.

Over the past decade, simulation has played a growing role in surgical education and may answer many of the training and verification needs within the current and future competency paradigms. Through several carefully performed validation studies, it is clear that simulator-based training conducted using sound education principles reliably results in skills which transfer to the operating room, improve performance, and decrease errors.[9–11] Unlike practice during real operations, simulators offer unlimited opportunities for practice with no chance of harm to patients. Training outside of the operating room is also cost-effective and can be successfully conducted in a self-study fashion, without being limited by the 80-h workweek.[9,12,13] Although many high-fidelity virtual reality simulators are now available for gastrointestinal and other operations, simulators need not be overly sophisticated to achieve educational benefit; indeed, low fidelity simulators have proven equally effective in fostering skill acquisition.[14]

Table 1 ACGME Core Competencies

Six core competencies
Medical knowledge
Patient care
Interpersonal and communication skills
Professionalism
Practice-based learning and improvement
Systems-based practice

Importantly, validated performance benchmarks for many simulators are now available, enabling their use for assessment purposes. The system that has undergone the most extensive validation is the Fundamentals of Laparoscopic Surgery (FLS) program, which was introduced by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the American College of Surgeons (ACS) in 2004.[15,16] Notably, the FLS program contains both skills (box-trainers) and cognitive (CD-ROM) components and comprehensively addresses areas relevant to the safe performance of laparoscopic surgery. Pass-fail thresholds have been established for both components, and a certification process now exist.[16,17]

Realizing the unique opportunity for using simulators as powerful educational and assessment tools, the ACS recently introduced the program for accreditation of Regional Education Institutes.[18] The overreaching goal of this program is to ensure that standards are met for curriculum implementation with appropriate quality assurance and long-term follow-up of the learner. Hence, the ACS program aims to establish a network of high quality facilities that will share resources, further develop effective teaching strategies, and conduct multicenter research with large cohorts of subjects. Similarly, the RRC in Surgery has mandated that all residency programs have skills curriculum by 2008 for accreditation. Thus, considerable momentum in simulation-based training has been gained.[19]

One of the main obstacles to widespread implementation of known best practices for simulation-based training is the lack of standardized methods and equipment. While the ACS accreditation program will likely address some aspects of this situation over time, recent studies suggest that a large gap exists. In one study, a survey was sent to the 253 residency training programs in the USA in 2004 regarding skills laboratory availability and usage.[20] Of the 162 (64%) programs which responded, only 55% had a skills laboratory and only 55% of these had mandatory attendance, suggesting that many of the facilities were not being used as a routine part of training. Moreover, equipment, staffing, and training practices varied widely, and no standardized curricula were being used across institutions. In a more recent study, a similar survey was sent to 40 program directors of institutions known to have skills laboratories.[21] Of the 34 (85%) programs that responded, only 62% had a documented curriculum, and again, equipment, staffing, and training practices varied widely. Importantly, 100% of the programs indicated that they supported a national skills curriculum.

ACS/APDS National Skills Curriculm Overview

As evidenced by the wide variety of training practices and the large body of simulation literature describing numerous

Table 2 National Skills Curriculum Phases and Launch Dates

Phase		Date
I	Basic/core skills and tasks	July 2007
II	Advanced procedures	January 2008
III	Team-based skills	July 2008

unsynchronized task development efforts by individual groups, there is an obvious need for a standardized curriculum. Such a curriculum would save many institutions the time, effort, and expense of repeating work that has already been done by others, and help to identify the best practices for various simulations that already have documented feasibility and benefit. Critical to this effort is selection of appropriate content, adherence to proven education principles, and wide dissemination of sufficiently detailed information such that curricula may be widely implemented without ambiguity.

In an effort to take on this daunting mission, the Surgical Skills Curriculum Task Force was established by the ACS and the Association of Program Directors in Surgery (APDS). Under the leadership of Gary Dunnington, M.D., Helen MacRae, M.D. and Debra DaRosa, Ph.D., this committee was formed in 2005, and numerous content experts were recruited. The committee's objective was to improve resident performance through skills practice and to use assessment of skills as a means of determining "operating room readiness." The committee formulated a plan to create a National Skills Curriculum in three phases with an ambitious timeline (Table 2). These phases were chosen to specifically address the ACGME core competencies (Table 1), many of which are difficult to teach and assess using conventional methods.[5] In particular, technical skills (often considered as part of patient care), interpersonal and communication skills, and professionalism may be effectively taught using simulation.

The curriculum is intended to be sufficiently robust to meet the RRC requirements, affordable, and portable. So that a maximal number of institutions may use the curriculum, an emphasis has been placed on using low cost simulators that are reproducible, reliable, and simple. There will be no cost for programs to use the curricular materials, which will include very detailed descriptions and instructions regarding the set up, performance, and assessment of the simulations. To aid in widespread availability, the curriculum will be web-based, such that content may be freely accessed. Such a system may ultimately be useful in performing large multicenter trials such that further improvements in training practices may be achieved.

The design of the curriculum is as follows. While there are certainly many ways in which any given surgical task or procedure may be performed, for practical reasons and to ensure uniformity, only one method will be included in the curriculum. To as large extent as possible, proven education principles will be used. From the psychomotor literature, it is clear that educational objectives can best be attained when practice is separated from performance, in this case the operating room. Distributed,[22] deliberate,[23] and structured[24] practice using performance-based endpoints[10–13] is an ideal method for teaching many technical skills using simulators. Such strategies enhance efficiency, as trainees only practice as much or as little as needed to reach a uniformly acceptable level of performance. Fatigue is avoided, and the durability of skill acquisition is maximized.[25,26] Video tutorials have proven beneficial and efficient in hastening skill acquisition, and may be effectively used to augment feedback by teaching error avoidance strategies.[27,28] The importance of this type of feedback, as well as formative and summative feedback provided through direct observation by proctors, cannot be overemphasized. One of the key training concepts is to foster recognition of mistakes such that problems may be anticipated and avoided, with decision-making integrated into the learning process.

Using these principles, a template for the curricular modules was established (Table 3). For any given module, it is envisioned that the trainee will review the video tutorial of expert performance and error avoidance strategies, undergo guided practice until the performance goals have been achieved, and then suitable performance will be verified. Assessment methods may include direct observation or video-based assessment using objective discrete performance metrics or one of several global rating systems.[29–31]Remediation can then be offered for individuals who do not meet the performance standards. The goal is to have residents "checked out" on a module with proficiency verified before going to the operating room. Hence, these programs aim to ensure "operating room readiness" for residents.

Table 3 Template for Modules

Established modules
Objectives
Assumptions
Suggested readings
Description of laboratory module
Description of steps for skill/task/procedure
Common errors, error prevention strategies, and error rescues techniques
Expert performance
Recommendations for practice
Supplies and recommendations for station set-up
Suggested time length for modules

Table 4 Twenty Modules Authored, Peer-Reviewed, and Accepted for Inclusion in Phase I

Phase I modules
Asepsis and instrument handling
Knot tying
Suturing
Tissue handling, dissection, wound closure
Advanced tissue handling, flaps and skin grafts
Catheterization, urethral and suprapubic
Airway management
Chest tube and thoracentesis
Central venous access, arterial lines
Surgical biopsy
Arterial anastomosis
Laparotomy, opening and closure
Principles Of bone fixation and casting
Inguinal anatomy
Upper endoscopy
Lower endoscopy
Basic laparoscopic skills
Advanced laparoscopic skills
Hand sewn anastomosis
stapled anastomosis

Phase I: Basic/Core Skills and Tasks

Thus far, 20 modules have been authored, peer-reviewed, and accepted by the committee for inclusion in Phase I, with a launch date of July 2007 (Table 4). It is expected that as new technologies are developed and new training practices are identified, modifications of existing modules and the introduction of additional modules may be needed. Further modifications may allow for greater interactivity and self-assessment by the resident learner. Fortunately, the web-based platform will readily lend itself to rapid content revision and distribution. While the scope of the curriculum is intentionally broad, many of the modules specifically relate to gastrointestinal surgery. To illustrate the content of the curriculum in some of these areas, descriptions of the basic and advanced laparoscopic modules (authored by Drs. Daniel Scott, Gerald Fried, and Daniel Jones) are listed below.

Basic Laparoscopic Module

This module is designed to teach basic laparoscopic skills and it includes three components, including (1) laparoscopic camera navigation using a camera navigation videotrainer system, (2) basic eye-hand coordination tasks using the Southwestern videotrainer stations, (3) additional laparoscopic tasks using the MISTELS Tasks 1–3 which are part of the FLS program, and (4) a cannulation exercise. This module describes a validated proficiency-based training curriculum for each component using established expert-derived performance levels based on objective, validated metrics for all tasks.[13,32,33] All three components use box-trainer technology (Figs. 1 and 2) which has proven reliable and cost-effective. While numerous validated virtual reality simulators are available, their use is associated with higher costs and increased maintenance, which currently preclude their inclusion in this module.

Figure 1 Videotrainer equipped with the five Southwestern Stations for basic laparoscopic skills.

Figure 2 FLS box-trainers equipped with tasks 1–5.

According to the template for the curriculum modules (Table 3), trainees are oriented and view the video tutorial for each task. Trainees undergo proctored pre-testing as a measure of baseline skill and then self-practice until at least two consecutive repetitions have been achieved at or beyond the predetermined proficiency level. Trainees then undergo proctored post-testing, for objective comparison of performance with baseline and verification of proficiency. Remediation is afforded to any individual who does not reach proficiency and proctors are available as needed for additional tutoring. Using this training strategy, we have consistently achieved excellent results.[12,13,25,26,33,34] Importantly, this strategy effectively trains even complete laparoscopic novices to a sufficient level of performance to pass the FLS certification examination.[13]

Advanced Laparoscopic Module

This module is designed to teach advanced laparoscopic skills and includes three suturing exercises, including (1) MISTELS/FLS Tasks 4 and 5 (interrupted suturing with intracorporeal and extracorporeal knot-tying), and (2) a continuous suturing exercise with intracorporeal knot-tying. All components use box-trainer technology, along with conventional laparoscopic needle drivers and suture. Previously established proficiency levels[13] are used in a similar fashion to the basic skill module and curricular implementation is identical.

Phase II: Advanced Procedures

Thus far, 15 modules have been selected by the committee for inclusion in Phase II, with a launch date of January 2008 (Table 5). While these modules are still being assembled, it is envisioned that the same format will be used and that whole procedures will be taught using available simulators and other available resources, including task trainers using ex-vivo animate models, live in-vivo animate models, and human cadavers. The goal of Phase II is to train residents on all relevant steps of a given procedure or operation in a nonthreatening simulated environment. Similar to Phase I, video tutorials, error avoidance strategies, and guided practice will be implemented. Verification of proficiency will rely more heavily on global performance assessments, which are conducive to procedural ratings.[29–31]

Table 5 Fifteen Modules Selected for Inclusion in Phase II

Phase II modules
Laparoscopic ventral hernia repair
Laparoscopic colon resection
Laparoscopic/open bile duct exploration
Abdominal wall stomas
Laparoscopic appendectomy
Laparoscopic nissen fundoplication
Sentinel node biopsy and axillary lymph node dissection
Open inguinal/femoral hernia repair
Laparoscopic inguinal hernia
Laparoscopic/open splenectomy
Laparoscopic/open cholecystectomy
Thyroidectomy
Parathyroidectomy
Gastrectomy
Distal/total pancreatectomy

Phase III: Team-based Training

While specific details are not yet available, several modules are planned for inclusion in Phase III, with a launch date of July 2008. These modules will provide team scenarios in the setting of the operating room, the trauma bay, and the surgical intensive care unit. Team-based training is the next frontier in surgical simulation (Fig. 3), as evidenced by recent reports that indicate the utility of this strategy in teaching and assessing decision making, communication, and professionalism.[35,36] By including multidisciplinary members of the operating team (surgeon, anesthesiologist, scrub, circulator), a unique opportunity exist to replicate both routine situations, as well as potentially rare adverse events, in a safe environment where numerous interactions can be monitored. Through lessons learned from aviation, crew resource management principles may be applied and participants can be effectively taught using briefing and debriefing approaches.[37,38] While this field is still in its infancy, there is a profound potential to dramatically enhance the training of the entire health care provider team and thereby positively impact the delivery of optimal patient-centered care.[1]

Assessment of Performance

In the past, the most reliable methodology for assessment of skills learned in the surgical skills laboratory has been the Objective Structured Assessment of Technical Skills (OSATS) examination, a multistation exam with faculty observers.[30] The faculty intense nature of this examination has limited its more widespread utilization. This new curriculum will provide an alternative methodology for assessment using verification of proficiency modules.[29] Eleven modules have been developed; each with recommendations for guided practice with performance standards to prepare for a video of a learner's performance. Videotapes will then undergo blinded review by expert faculty with either a "pass" or "needs more practice" final assessment. Verification of proficiency in this methodology is equivalent to operating room readiness.

Guidebook for Program Directors

Another key component of the curriculum package is being developed by Debra DaRosa, Ph.D. This element will provide an overview for Program Directors implementing or revising surgical skills laboratory programs. It will offer various curriculum models as well as an overview of motor skills training that will be useful in faculty development for teaching in the skills laboratory. This guidebook will provide comprehensive lists of vendors as well as materials to support the evaluation of the program and resident performance.

Where Does Virtual Reality Fit into the Picture?

Virtual reality trainers have been used successfully for training skills relevant to gastrointestinal surgery for over a decade, with strong validation data for several systems.[10,39–41] However, many centers have experienced frustration with virtual reality technology from both financial and practical standpoints. Certainly, initial cost can be quite high (over $100,000 for laparoscopic cholecystectomy simulators with haptic feedback), and system maintenance and periodic (every 1–2 years) software updates are associated with additional cost. Historically, some systems have been plagued by reliability issues, in terms of mechanical (interface, handles, etc.) or software malfunctions, whereas more recently improvements have been made. For many programs, acquiring such expensive equipment is simply not feasible. Indeed, simply having sufficient funding to support the manpower needs of a skills laboratory is a sizeable challenge for most institutions. Nonetheless, for programs with more abundant resources, often purchasing only a single simulator may be feasible. This situation may leave educators especially vulnerable should equipment failures be encountered during critical training periods. Curricula are frequently designed to becompleted within a period of several months, with other courses scheduled in a time-sensitive fashion, as part of a larger integrated curriculum, which must be completed within an academic year. Additionally, it is quite difficult logistically to train numerous individuals on a single simulator due to scheduling issues. For these reasons, having numerous low-cost inanimate and box-trainer simulators is often a more attractive option.

Currently, there are also limitations in using virtual reality systems for assessment purposes. In part, this is due to a lack of established methods for using virtual systems in an optimal fashion in this context. Unlike box-trainers, virtual systems tend to have a much more significant interface issue, whereby a more significant extent of "gamesmanship" is required. Whereas validated box-trainer tasks, such as FLS, may be reliably used to measure performance based on only a single repetition,[17] virtual systems seem to require a more prolonged warm-up period for the participant to understand and overcome the nuances of the system.[42] For some systems, the metrics have not demonstrated construct validity, which is usually measured by a simulator's ability to discern novices from experts according to performance scores.[41] Accordingly, such metrics cannot be used for proficiency-based training, since an expert-derived performance score may be inaccurate. Similarly, if valid metrics are not employed, reliable assessment is not possible. While

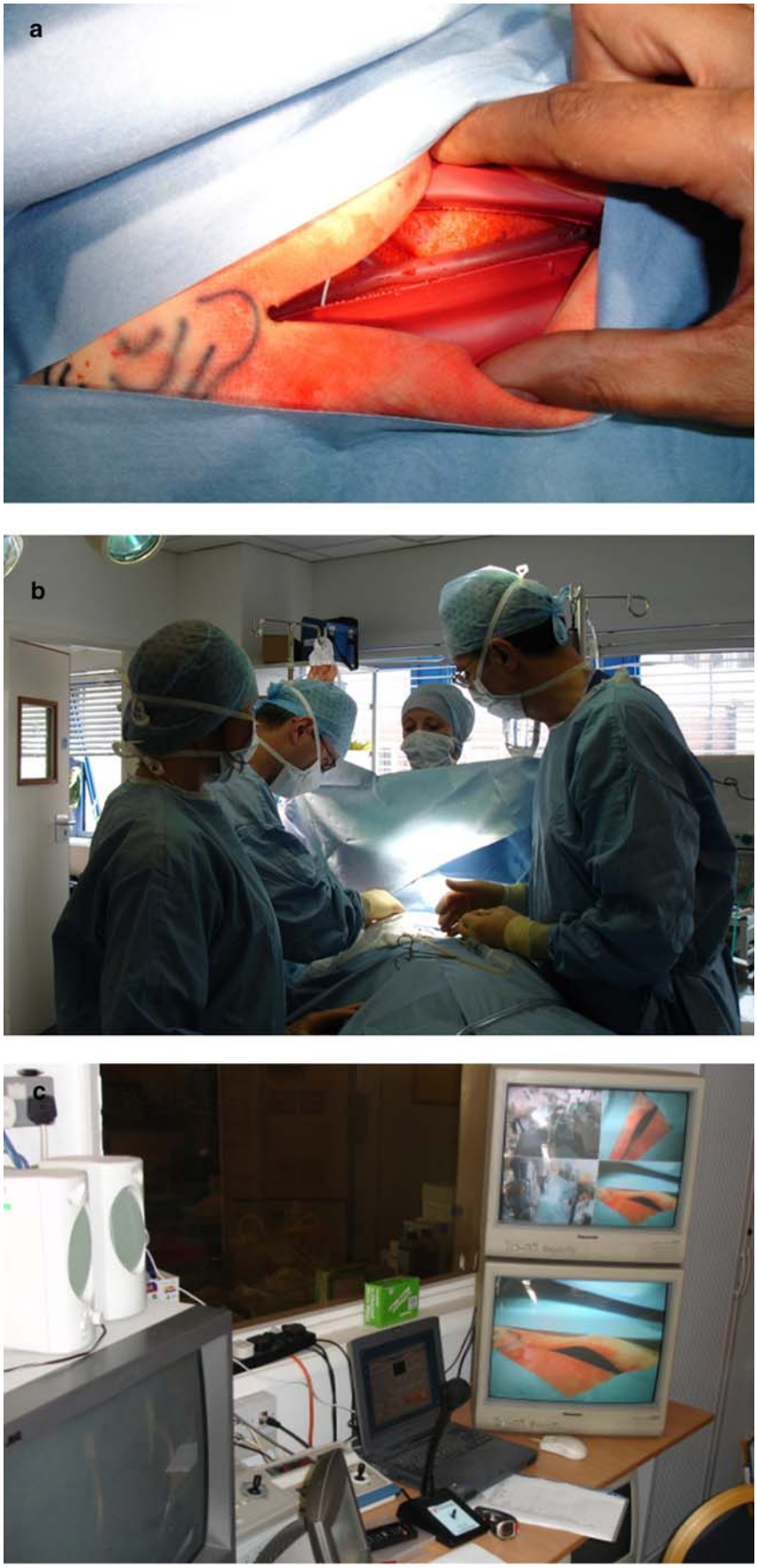

Figure 3 The virtual operating theatre used for team training at the Imperial College School of Medicine in London. Members of the operating room team fully replicate a carotid endarterectomy procedure using a latex model (**a**) and a simulated patient (**b**) while being monitored by proctors in the control room (**c**).

all virtual reality simulators do not suffer from these shortcomings, this technology is still in evolution. Much needed investigations and work in these areas is underway.

By the same token, the potential value of virtual reality simulators is tremendous. For whole procedures, it is impractical to build a different inanimate trainer for each procedure that needs to be simulated. Animal and cadaver model alternatives are not nearly as cost-effective as we might like. Thus, within this domain, virtual trainers will likely find utility, especially if models for containing costs or sharing resources are further developed. Moreover, as Dr. Rick Satava has championed, only in virtual reality worlds will we be able to realistically replicate patient-specific anatomic information, derived from CT or MRI datasets.[43] This type of technology will someday allow surgeons to have dress rehearsals of various operative approaches in a virtual trainer before performing the real procedure.

However, for some areas at present, virtual reality simulators may be very important. Similar to the FLS program, work is underway by a SAGES task force to develop the Fundamentals of Endoscopic Surgery (FES) program, designed to teach and assess knowledge and skills related to flexible endoscopy. This committee is evaluating endoscopy simulators and hopes to use a simple and inexpensive platform similar to the FLS box-trainer. However, low fidelity simulators for flexible endoscopy may not be robust enough for these purposes. Although expensive, virtual reality GI endoscopy simulators replicate many aspects of the real procedures that are of interest to the committee and are therefore being considered. Indeed, there is precedent for the use of complex virtual reality simulators such as these; endovascular simulators are sufficiently robust such that their use has been adopted as part of the US Food and Drug Administration (FDA) training requirement for carotid stenting procedures.[44]

Setting the Standards for Practicing Surgeons

In just over a decade, we have seen the face of modern surgical education change dramatically. Over this same time period, technology for surgical procedures has exploded, with new techniques and procedures being continually introduced. Who would have thought that transvaginal cholecystectomy would be a promising new procedure?[45] Given the climate of close scrutiny by the public, regulating bodies, and others, practicing surgeons will likely be required to undergo more rigorous verification of proficiency in the future. Indeed, the ABS has already made headway with its Maintenance of Certification Programs to institute quality assurance through the use of database outcomes. Although current efforts involving simulation are predominantly geared towards resident education and assessment, these strategies are likely to be used for practicing surgeons as well. It is apparent that current training models using weekend courses or even minifellowship programs still fall short of desired goals for surgeons wishing to acquire new skills and to adopt new procedures into their practice.[1] One study regarding proficiency-based laparoscopic suturing suggests that simulators may be successfully used in the setting of a continuing medical education (CME) course format.[46] Such courses may augment efforts geared towards proctoring practicing surgeons during supervised patient care experiences. In the not-so-distant future, verification of proficiency using simulation-based assessment may be required for certification or credentialing purposes.

Conclusion

The ACS/APDS National Skills Curriculum is well underway and will serve as a vital part of enhancing resident education through simulation. This model is well positioned to rapidly fill many of the gaps that exist across programs by freely offering well designed, standardized curricula in numerous domains, including gastrointestinal surgery. By implementing uniformity in training and assessment of core competencies, residents will be better prepared for their subsequent patient encounters and careers. These methods will likely be useful for assuring competency of practicing surgeons as well.

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Integrating Simulation in Surgery as a Teaching Tool and Credentialing Standard

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Abstract The time-honored training methods of surgery are rapidly being replaced with new teaching tools that are being integrated into residency and recredentialing standards. Numerous factors including societal, professional, and legal have all forced surgical training programs to seek alternative methods of training residents. Learning theories that have provided the basis for open surgical skills training have been modified and culminated in the theory of automaticity and the "pretrained" laparoscopic novice. A vast array of simulators exist for training, ranging from inanimate video trainers, human patient simulators, to more recently virtual reality (VR) computer-based trainers. Currently, inanimate trainers are deployed widely throughout surgical training programs and serve as the primary platform for laparoscopic skills training. As technology evolves, VR systems have become available, allowing for more complex skills training with realistic computer-generated anatomic structures. Using the theories of crisis management and crew resource management, simulation is moving from simple skills training to whole-team training in mock operating room environments. Looking to the near future, medical training will continue to evolve to meet the changing demands of society and professional responsibility to ensure patient safety. With the advent of accredited skills-training centers endorsed by the American College of Surgeons, simulation will be the catalyst for these continuing changes.

Keywords Surgical simulation · Review · Surgical education · Patient safety

The apprentice model of medical training dates to antiquity when Egyptians would apprentice young boys to become "master mechanical healers."[1] Modern surgical training in the USA credits Dr. William S. Halsted, who in 1889 established an educational system of graded learning in which surgical trainees would, over time, do more and more of an operation as their training progressed.[2,3]

Today, diverse factors ranging from the rising cost and complexity of medical technology, resident work hour restrictions, decreased reimbursement, and an increasingly hostile malpractice environment have all culminated in forcing major changes in the way that modern surgical trainees are educated.[2–4] Further, the National Academy of Science's Institute of Medicine reported that approximately 44,000 to 98,000 deaths occur each year due to medical error and thereby challenged the profession to rethink the existing medical educational system.[5]

The traditional apprenticeship model of graded learning starts with basic skills like tying a series of knots, evolves to performing simple procedures, and culminates with complex operations. However, these "open" skills are often not transferable to laparoscopic procedures. The master "open" general surgeon may not be able to perform laparoscopic procedures safely. Laparoscopy uses fixed ports with elongated instruments denying the surgeon the tactile feedback encountered in open surgery. Additionally, because most video systems are only two dimensional, the surgeons' depth perception and peripheral vision are restricted.

The ability to tie a traditional two-handed knot does not mean the surgeon can tie an intracorporeal laparoscopic knot. Learning these techniques in the operating room (OR) may represent a patient safety issue and may prove too

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costly for the hospital; therefore, new techniques and ideas about how to train surgeons are evolving.

Learning Theory

Most teaching curricula are based on constructivism, meaning "learning by doing" or "experiential learning". This theory, described by Kolb, states that knowledge is created by the "transformation of experience, an active process where a four-stage cycle translates experience, through reflection, into concepts." The concepts serve as a basis for future experimentation creating a "continuous feedback loop" that solidifies learning.[6,7] In addition to Kolb's theory, Aggarwal et al.[7] developed a three-stage theory to explain motor skills acquisition. The three stages describe a continuum of "cognition" followed by "association" and finally "automation" where the learner is taught the task, practices the task, and finally performs the task "automatically".

Gallagher et al.[8] emphasized the importance of automaticity in simulation task training and advanced the idea of the "pretrained novice." Since learners have limited attentional resources, simulation training involving task training can prepare a novice surgeon to the point where they "automate" many of the basic psychomotor skills required to perform laparoscopic surgery. The "pretrained novice" can devote more cognitive resources to learning the steps of the procedure, learning how to handle or avoid intraoperative errors, and ultimately better assist the expert surgeon to perform safer surgery.

Reznick and MacRae[2] in a recent article on surgical simulation described the range of simulators available to include inanimate video trainers (VT), live tissue, cadaver, human patient simulators (HPS), and virtual reality (VR) computer-based simulators. Animals and cadavers were popular in surgical training until box trainers were developed, encompassing laparoscopic video equipment.

In 1997, researchers at the University of Texas Southwestern Medical Center hypothesized that intense training on inanimate models could actually improve operative performance. They tested second- and third-year surgical residents in a skills lab and in the OR. Trainees were pretested performing a set of tasks on VT and were evaluated while assisting on a laparoscopic cholecystectomy. Half the trainees were formally trained in the skills lab practicing 30 min daily for 10 days. The other group had no additional formal skills training. After 30 days, all subjects were again tested in the VT as well as during their performance of a laparoscopic cholecystectomy. The five tasks included the checker board, bean drop, triangle move, run rope, and endostitch (Fig. 1). Performance of a laparoscopic cholecystectomy was assessed by surgeons

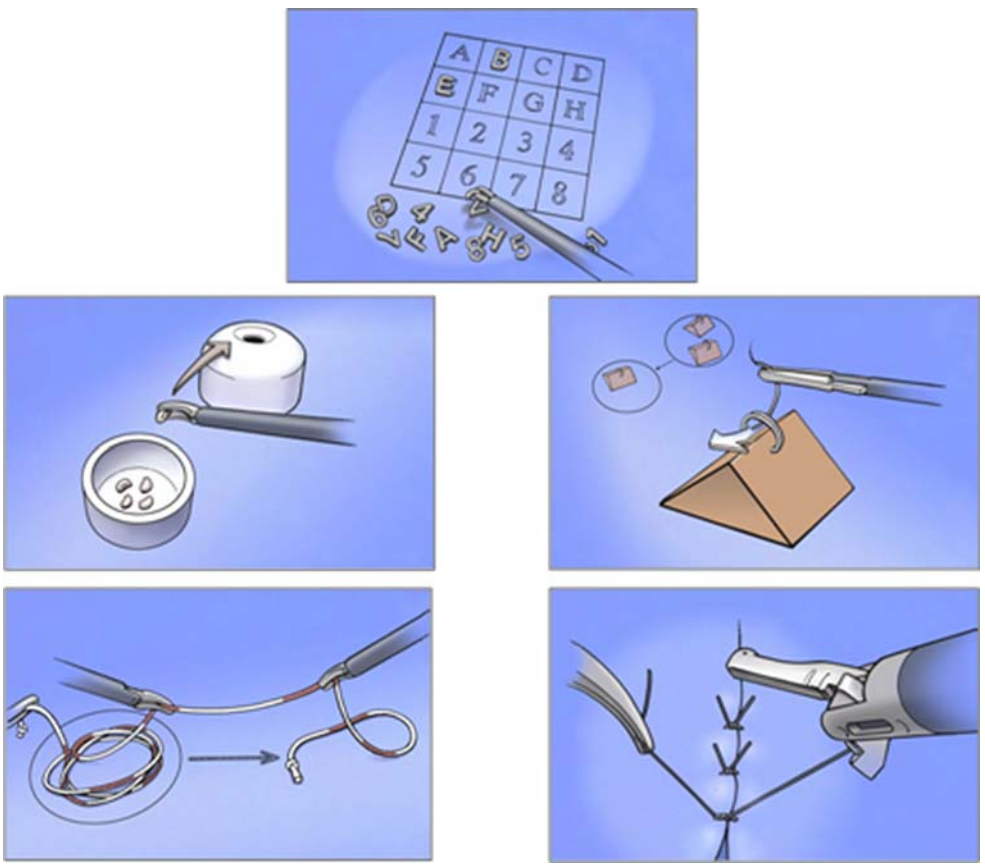

Figure 1 Five tasks—the checkerboard, bean drop, triangle move, run rope, and endostitch.

blinded to whether residents trained in the skills lab using a Likert scale: (1) respect tissue, (2) time and motion, (3) instrument handling, (4) knowledge of instruments, (5) flow of the operation, (6) use of assistants, (7) knowledge of specific procedure, and (8) overall performance. Data from these studies indicated that the VT-trained group improved their task performance and, more importantly, the ability to perform a laparoscopic cholecystectomy compared to those who did not formally train in the skills lab.[9]

In another study using an inanimate model for laparoscopic inguinal hernia training, Hamilton et al.[10] demonstrated that residents who trained on an hernia model significantly improved intraoperative performance as assessed by a validated global assessment tool compared to standard training. This study was important in that it established not only an inanimate model for training laparoscopic hernia but provided trainees with a curriculum (CD ROM based) that also improved cognitive knowledge.

Surgical box trainers and models have evolved into computer-based VR trainers. Currently, these systems train individual tasks, but new technology is on the horizon that will allow whole procedure training. Expanding on their prior work demonstrating that inanimate VT improved intraoperative performance, Hamilton et al.[11] studied the impact of task training on 50 surgical trainees randomized to either a VT or VR trainer. The effect of task training was assessed via pre- and posttest assessment on VT, VR, and intraoperative assessment during laparoscopic cholecystectomy. Both VR- and VT-trained subjects improved posttest performance, and interestingly, the VR group performed significantly better when tested on VT tasks. Operative performance improved only in the VR training group ($P< 0.05$). This critical study was one of the first to demonstrate improvement of psychomotor skills and intraoperative performance after training on VR systems, underscoring the importance of such systems for the training of surgeons.

Seymour et al.[12] prospectively randomized surgical trainees to VR training on the Procedicus MIST-VR trainer versus standard training and assessed in a blinded fashion intraoperative performance during laparoscopic cholecystectomy. Tissue dissection was 29% faster for VR-trained residents compared to the standard-trained (mentor–trainee) controls. Further, mean errors were six times less likely to occur in the VR trained group compared to controls. These data suggest that not only the speed of an operation but more importantly patient safety, quantified as decreased surgical error, may be improved with use of surgical simulation.

Once a task is trained to proficiency, it must be maintained. Additionally, when complex tasks such laparoscopic suturing are taught, it becomes important to understand how continued training is necessary before skills degrade to unsafe levels. In order to assess the ability of a subject to maintain surgical skills, Stefanidis et al.[13], studied medical students who were trained to laparoscopically suture to proficiency on the Fundamentals of Laparoscopic Surgery (FLS) VT system. Subjects were randomized to no additional training or serial training over several months. Overall, initial massed training improved the performance of both groups; however, ultimately the serially trained group performed the suture task significantly better compared to the massed-trained group. This study was instrumental in defining that for complex laparoscopic skills, it is essential to serially train to proficiency rather than rely on massed-training events. Additionally, it is the first study to suggest that proficiency in laparoscopic surgical skill is lost after a finite period of time—3 months time.

Other groups have focused on the interface of the technology with surgeons. Cao et al.[14] investigated the impact of haptic feedback and cognitive load during task training on a VR system (MIST-VR) compared to hybrid VT system (ProMIS). Subjects were stratified by post graduate year (PGY) level and tested during a transfer task. A cognitive load (math problems) was given during task training with and without haptic feedback. Results demonstrated that cognitive loading slowed speed and accuracy of performance, but subjects performed 16% faster and 97% more accurately with haptics than without, even while cognitively loaded. These results suggest that haptic feedback not only counters the effect of cognitive loading but also enhances performance. Given that most current commercial simulators lack haptic feedback, the findings of this study suggest that haptic feedback should be an important component for incorporation into future simulator technology.

Types of Simulators

A wide variety of simulators are available for training in gastrointestinal surgery. As computer technology has improved in performance and cost-efficiency, so to have the simulator systems. To be effective educational tools, simulators must be reliable and valid[15] (see Table 1). Whether a simulator is deemed valid or not generally requires numerous studies so that sufficient data can be accrued. Much of the research in simulation is appropriately focused on establishing the reliability and validity of various devices. On a practical level, simulators must also be cost effective and easily integrate into surgical education curricula.

Numerous examples of VT systems exist for training of general surgery skills. One of the earliest VT systems to be commercially available was the “Preceptor” system developed by Ethicon Endosurgery in 1995.[16] Since then numerous systems have been developed. The two most important systems currently are the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) FLS system and the Top Gun Laparoscopic Skills and Suturing

Table 1 Definitions of Reliability and Validity used in Studies of Surgical Simulation Adapted from Scott DJ, Virtual Reality Training and Teaching Tools, Mastery of Endoscopic and Laparoscopic Surgery, 2nd Edition

Definitions of Reliability and Validity used in Studies of Surgical Simulation	
Reliability	The precision of a devise
	Robust and durable to afford Consistent practise so that results are reproducible
	statistically scored from 0 to 1.0, between R=0.5 and 0.8 is moderate, >0.8 is high
Validity—the simulator's ability to measure what it was designed to measure	
Content validity	The extent to which all relevant dimensions within a given domain are measured
Constract validity	The ability to detect differences between groups with different levels of competence,
	supporting the motion that the test is measuring what it claims to measure
Concurrent validity	Results of the test correlate with the criterion standard known to measure the same domain
Predictive validity	Capacity to predict future performance
Face validity	Extent that the simulation resembles the real task

program. These systems are not just physical box trainers but rather represent validated tools for the development of both didactic knowledge and psychomotor skills necessary as a basis to perform laparoscopic surgery.

The FLS examination is a comprehensive education system consisting of three components: a box trainer, a computer based curriculum, and an assessment component (http://www.flsprogram.org/index.php). FLS evolved from the Mcgill Inanimate System for Training and Evaluation of Laparoscopic Skills (MISTELS) developed by Dr Gerald Fried at Mcgill University.[17,18] MISTELS consists of five psychomotor skills: peg transfer, pattern cutting, ligating loop, and intra- and extracorporeal knot-tying tasks (see Fig. 2). The didactic teaching and assessment module is designed to teach and assess knowledge of basic concepts, physiologic consequences, and complications of laparoscopy.

In 1997, SAGES launched an effort to create a system that would teach and assess the competence of surgeons to perform basic laparoscopic skills. In 2006, the FLS system was validated in multi-institutional study by Swanstrom et al.[17] The researchers evaluated the construct validity of FLS by asking three questions: could FLS discriminate in terms of cognitive and manual skills between surgeons stratified according to PGY level of training, experience level (number of cases performed of 12 specific operations), and finally based on a self assessment of competency? Overall, the study demonstrated that FLS reliably discriminates between groups for both cognitive and manual skills assessments.

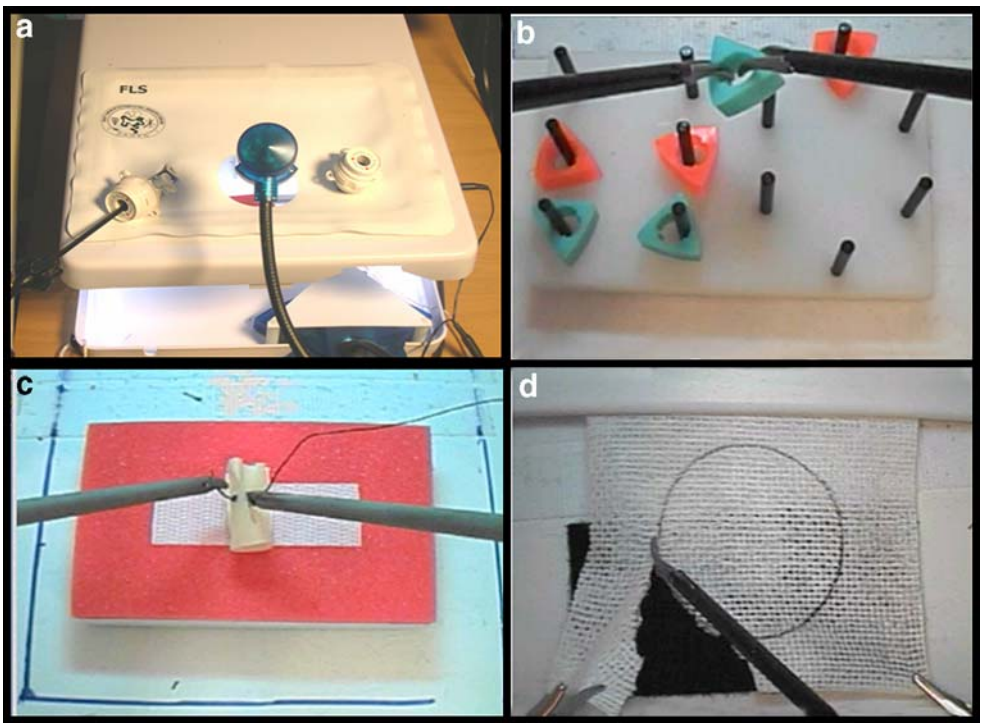

Figure 2 FLS box trainer system (**a**) with examples of tasks: **b** transfer task, **c** intracorporeal suture task, **d** precision-cutting task.

Internal reliability of the cognitive skills assessment was 0.81 and 0.88 for the manual skills assessment. This study is important in that it validates FLS as the first widely available education assessment system for determining a "minimum level of competence" in the field of laparoscopic surgery. The impact of this accomplishment is not to be underestimated. Even before this study was completed, FLS had been adopted by numerous surgical training programs, institutions, and the Department of Defense as a means of objectively assessing minimum competence for surgeons performing laparoscopy.

The Top Gun system was developed at Yale University by Dr. James Rosser. The system is taught as a massed course event over 2.5 days using a VT system and an intracorporeal suturing algorithm that deconstructs the steps of the task. The deconstruction of the task represents the real power of the system. Subjects practice drills which include the rope drill, cup drop, and triangle drill in preparation for the suture drill (see Fig. 3). In a study published in 1998, Rosser et al.[19] compared the performance of trained surgeons to residents with limited laparoscopic skills who participated in Top Gun training course. Results demonstrated that resident performance equaled or exceeded that of trained surgeons after Top Gun training. The authors concluded that structured training using a deconstruction of task algorithm was an effective means of training basic and complex laparoscopic skills.

Pearson et al.[20] published a study that investigated the effect of different training platforms, i.e., VT and VR systems (MIST-VR) as well as structured versus unstructured instruction, to teach an intracorporeal suturing task using the Top Gun algorithm. Results demonstrated that structured training was more effective than unstructured. In terms of the platform, both VT and VR systems were effective for training. The authors stated the VR system had an added benefit in that it provides a means for additional objective assessments based on the internal assessment metrics of the VR system.

The strength of both the FLS and Top Gun systems is that they have been validated in studies using large numbers of subjects, provide defined curricula for both cognitive and manual skills education, and are very cost effective compared to other available modalities (live tissue, cadaver, or computer-based systems) for teaching laparoscopic skills. Despite these strengths, these systems do not teach the learner whole surgical procedures. Additionally, they do not proctor the learner, thus requiring faculty input on avoiding and correcting errors.

Several studies have demonstrated the potential of VR simulators to teach basic and complex laparoscopic skills. Additionally, preliminary studies demonstrate that VR-

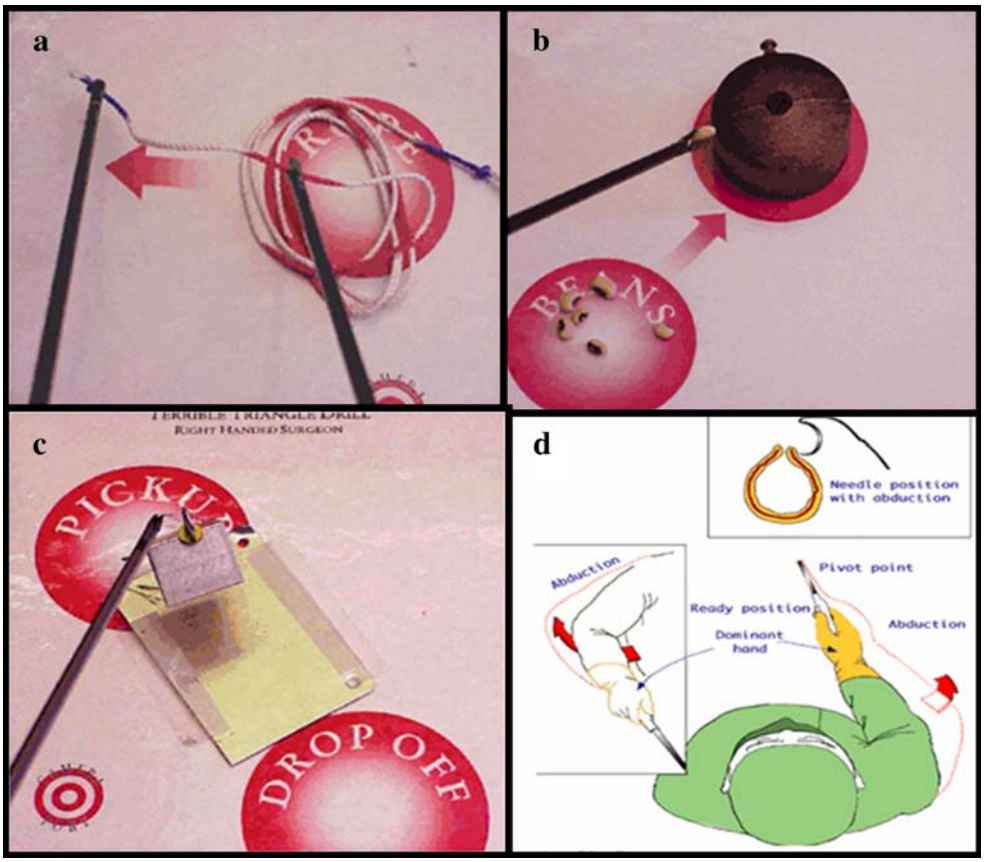

Figure 3 Top Gun practice drills: **a** rope drill, **b** cup drop, and **c** triangle drill in preparation for the **d** suture drill.

trained skills may be transferable and lead to improved performance intraoperatively compared to standard training. One of the limitations of VR task trainers for general surgery training is the lack of uniformity in design, execution, and metrics of assessment. Two recent articles have reviewed the current state of VR simulation. Sutherland et al.[21] from Australian Safety and Efficacy Register of New Interventional Procedures of the Royal Australian College Surgeons (ASERNIP-S) and Carter et al.[22] from the Working Group for Evaluation and Implementation of Simulators and Skills Training Programmes of the European Association of Endoscopic Surgeons (EAES) looked at the available VR systems in meta-analysis, finding that in general, VR system improved subjects' performance but that overall, VR simulators are no better compared to other simulation technology such as VT. Summarized reasons for these finding are included in Table 2.

In a recent editorial on the topic of medical simulation in surgery, Dutta et al.[23] placed the issue of the validation of simulation technology into a broader context. The authors raised the question whether a comprehensive strategy of competency-based training, using multiple modalities including simulation and supervised clinical care, yields better outcomes for patients, fewer errors, or more efficient patient care and education than does the current system of mostly apprenticeship-based training. The importance is not whether simulators are a superior means of training but "rather if simulation as part of a competency-based curriculum is an effective pedagogical (teaching) strategy as compared to the current apprenticeship-based system." Furthermore, the authors underscored that what is possible via simulation training will only be realized if government, industry, and academia continue to partner in ways that make the research and development cost effective.

Several VR simulator companies have developed software modules that allow for the practice of whole procedures. These include both total VR systems and hybrid systems that combine both VR with physical interfaces.

Simbionix's (Lod, Israel) Lap Mentor™ surgical trainer (http://www.simbionix.com /LAP_Mentor.html) has a variety of procedural modules that include a laparoscopic cholecystectomy, a ventral hernia, and a Rou-en-y gastric bypass (Fig. 4). Face validity was established for the Lap Mentor™ by Ayodeji et al.[24] To date, neither construct nor concurrent validity has been established for the Lap Mentor™.

Surgical Science's (Gothenburg, Sweden) LapSim® surgical trainer (http://www.surgical science.com/index.cfm/en/products/), in addition to its basic skills module, has a software module for a laparoscopic cholecystectomy called the LapSim® Dissection (see Fig. 5). Two recent studies[25,26] have established construct validity for the LapSim. Concurrent validity has not been established for this system.

Additionally, other systems like SurgicalSim's® (Oslo, Norway) Surgical Education Platform (SEP) trainer (http://www.simsurgery.com/products.htm) allow for suture practice during laparoscopic fundoplication procedures (see Fig. 6). However, no studies have established face or construct validity for the SEP trainer to date.

A hybrid system has been developed from the original ProMIS™ system (http://www. haptica.com/index.htm) by Haptica (Dublin, Ireland) that allows for whole procedure training (see Fig. 7). This novel system allows subjects to complete a laparoscopic colon procedure using actual instruments and simulated physical tissues all through a VR interface. Two studies[26,27] have demonstrated construct validity of the ProMIS™ system. Concurrent validity for intraoperative performance has not been established to date.

Crisis Management

The simulation movement in surgery has expanded from the realm of technical task trainers to the pursuit of completely simulated OR environments for the training of surgical teams in both technical and nontechnical performance. The integration of HPS and OR personnel fosters comprehensive training of surgical crisis management (SCM) and crew resource management (CRM) in the mock OR. These environments are simulated only in the sense

Table 2 Critique of VR Simulation Studies from Meta-analysis

Sutherland et al.[22]	Carter et al.[23]
Small sample sizes in all studies	Lack uniformity in information given to subjects during studies
Multiple and confounding comparisons	No consistent assessment of face validity of system of systems between studies
Lack of consensus on core surgical skills assessed	Stratification criteria of subjects not uniform
No consensus on definitions of "standard" training used for control groups	No consensus on assessment of predictive validity/ concurrent validity
Outcome assessment not blinded leading to bias	
Concurrent validity not established. Most studies measure simulator performance, not subject performance	

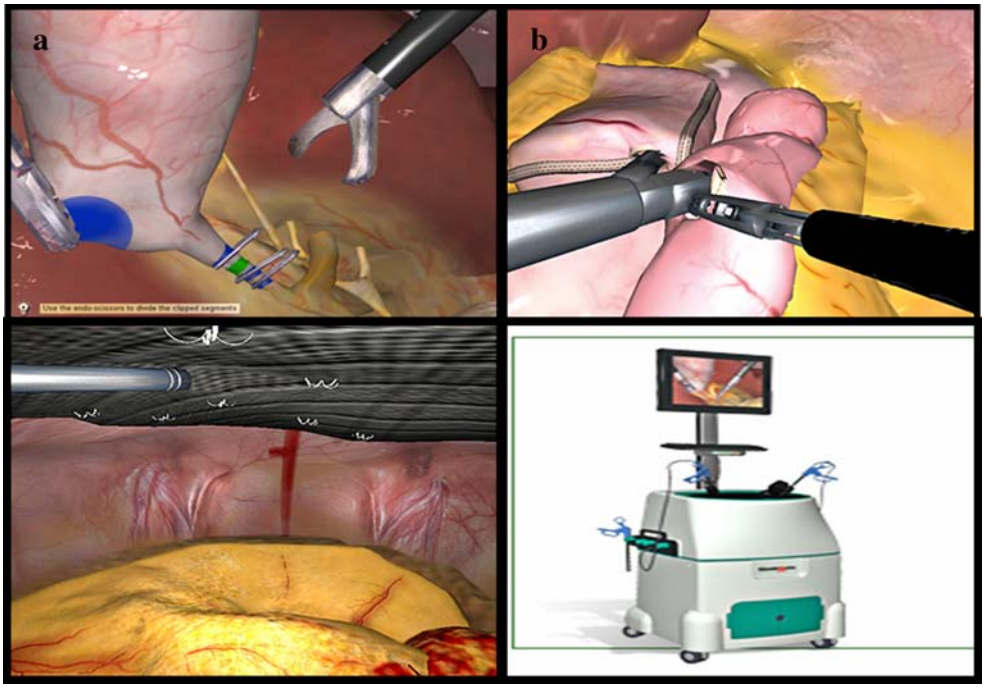

Figure 4 Examples of whole task VR modules for the Simbionix Lap Mentor™ surgery simulator. **a** Transection of cystic duct during laparoscopic cholecystectomy, **b** formation of gastrojejunostomy during laparoscopic gastric bypass, **c** placement of tacks in mesh during laparoscopic ventral hernia repair, **d** Lap Mentor™ trainer.

that the patient is a mannequin. The OR equipment and surgical instruments are not props, and the participating personnel are immersed in real, albeit scripted, OR scenarios.

The aviation industry first embraced the concept of CRM training. Healy et al.[28] reviewed the history of this type of training in the aviation industry and described its elements as they relate to performance in the OR envi-

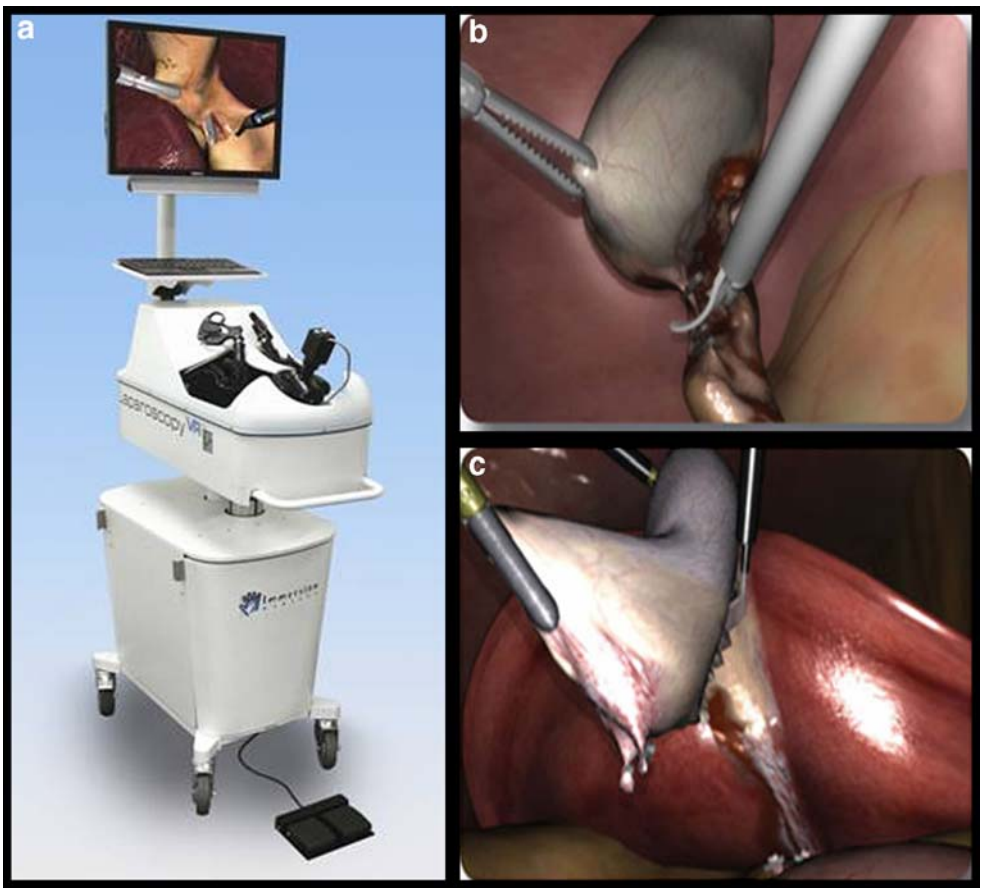

Figure 5 **a** Surgical Science's (Gothenburg, Sweden) LapSim® surgical trainer; **b**, **c** laparoscopic cholecystectomy module called the LapSim® Dissection.

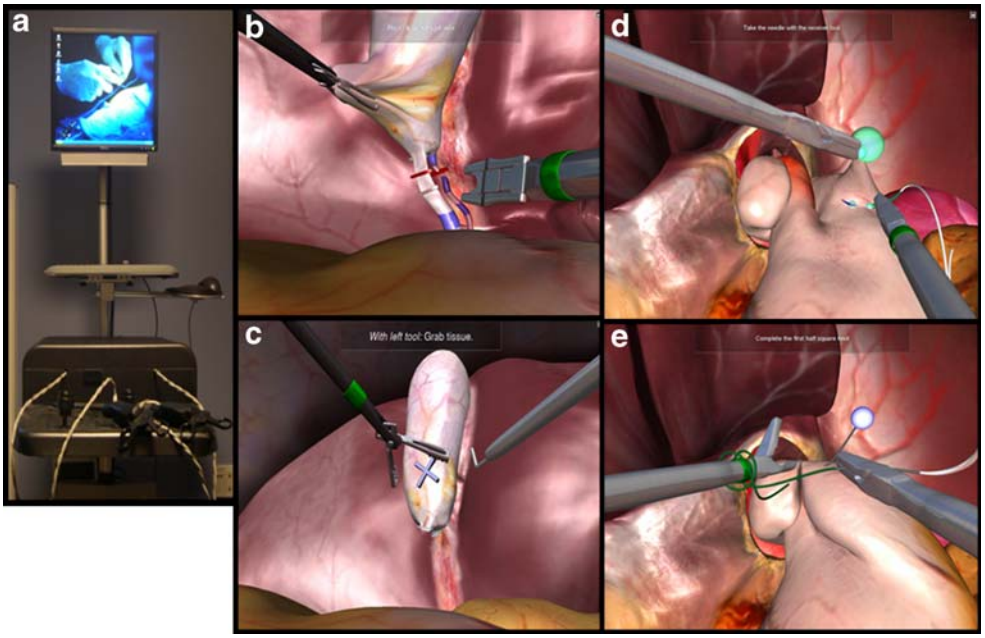

Figure 6 SurgicalSim SEP trainer (**a**), cholecystectomy (**b**, **c**), suturing task (**d**, **e**).

ronment. Aviation accidents occur not because of equipment failure but rather because crew members fail to work together efficiently during crises. Psychologists determined that crew members recognized problems early on but were reticent to bring them to their superiors' attention. Based on these findings, the aviation community implemented the following: (1) reducing emphasis on team hierarchy, (2) encouraging subordinate team members to immediately raise concerns related to safety, and (3) training senior team members to listen to subordinate team members and consider all concerns raised. Lessons learned in the aviation industry can be reinforced in the mock OR and during the debriefing sessions. Preprocedure briefs (OR final timeout), OR checklists, and the promotion of open team communication can be all practiced as part of effective OR interactions.

Mock Operating Room

From the Imperial College of London, Moorthy et al.[29] recently performed a validation experiment using a bleeding crisis in a simulated operating theater. The study assessed surgical residents' technical abilities and nontechnical team/human factors skills during crisis. The crisis

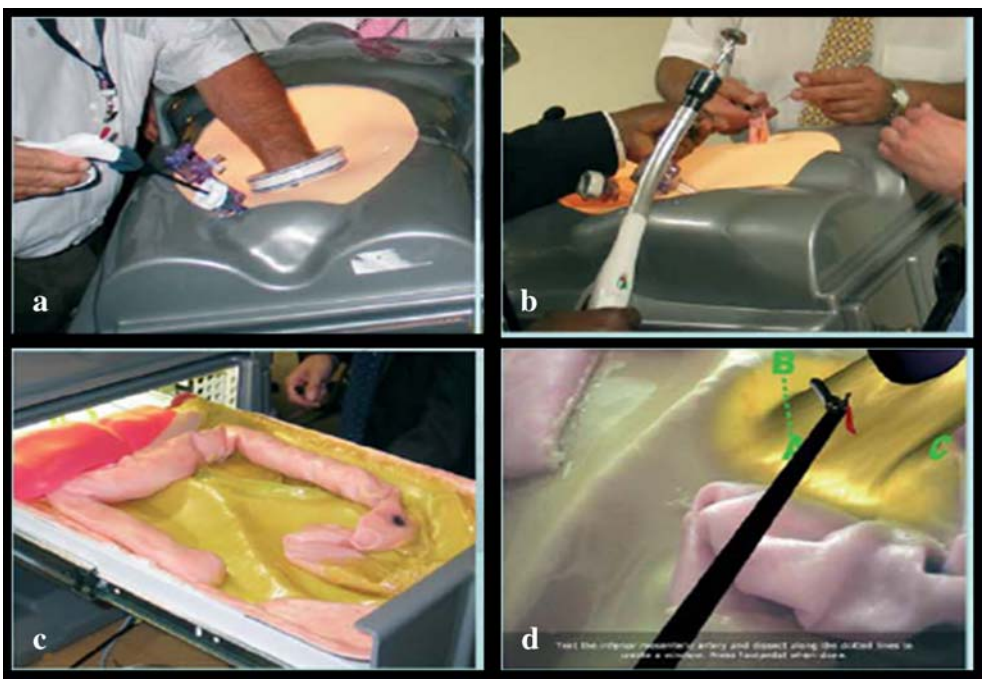

Figure 7 ProMIS LapColectomy allows subjects to complete a laparoscopic colon procedure using **a**, **b** actual instruments and **c** simulated physical tissues all through a **d** VR interface.

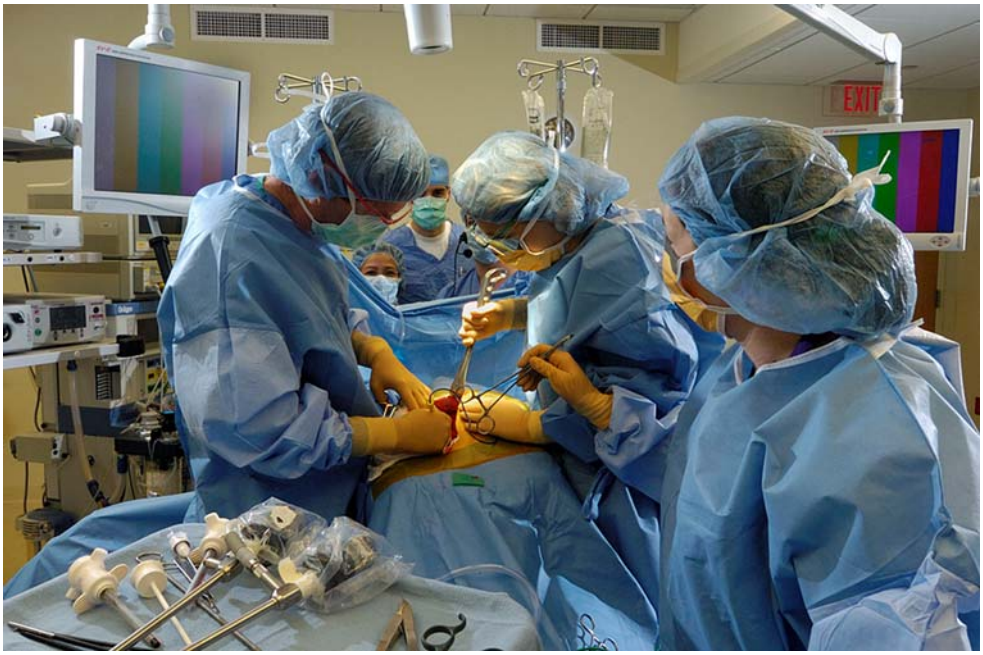

Figure 8 Conversion to open after a simulated laparoscopic surgical crisis, Shapiro Simulation and Skills Center, Beth Israel Deaconess Medical Center, Boston MA (http://www.bidmc.harvard.edu/sasc).

scenario involved the use of a synthetic model of a 5-mm femoral vein laceration mounted to an anesthesia HPS. A standardized OR team composed of an anesthetist, a scrub nurse, and a circulating nurse was used. Global rating scales were utilized to measure the technical and nontechnical performance of junior and senior surgical residents. Additionally, variables such as time to diagnosis, time to inform team members of crisis, time to achieve control, and closure laceration were recorded. The researchers found high face validity (95% agreement) for their mock OR scenario. Further, data showed good discrimination between the performance of senior and junior trainees during the bleeding crisis. No major differences were noted between the groups for nontechnical performance. Metrics of time noted several significant differences between groups including time to diagnosis of bleeding (P=0.01), time to control bleeding (P=0.001), and time to close laceration (P=0.001). This sentinel study was the first to describe the application of SCM/CRM techniques in a model of open surgery. Not only did the Imperial College's synthetic model have high face validity, but most importantly they developed and validated reproducible metrics to measure technical and nontechnical surgical performance.

At the Beth Israel Deaconess Medical Center's (BIDMC) Carl J. Shapiro Simulation and Skills Center (SACS) in Boston, MA, Powers et al.[30] established face, content, and construct validity for simulated laparoscopic crisis scenarios in a mock laparoscopic endosuite (see Fig. 8). We created a novel synthetic abdomen that allowed for placement of a Veress needle, abdominal CO2 insufflation, trocar insertion, and simulation of intraperitoneal hemorrhage (see Fig. 9). The synthetic abdomen was mated to a METI HPS. Physiologic parameters such as blood pressure, pulse, and oxygen saturation were controlled and displayed for participants on the anesthesia monitors after each operative intervention to create a realistic experience.

The study demonstrated high face validity for the laparoscopic model and the mock endosuite environment.

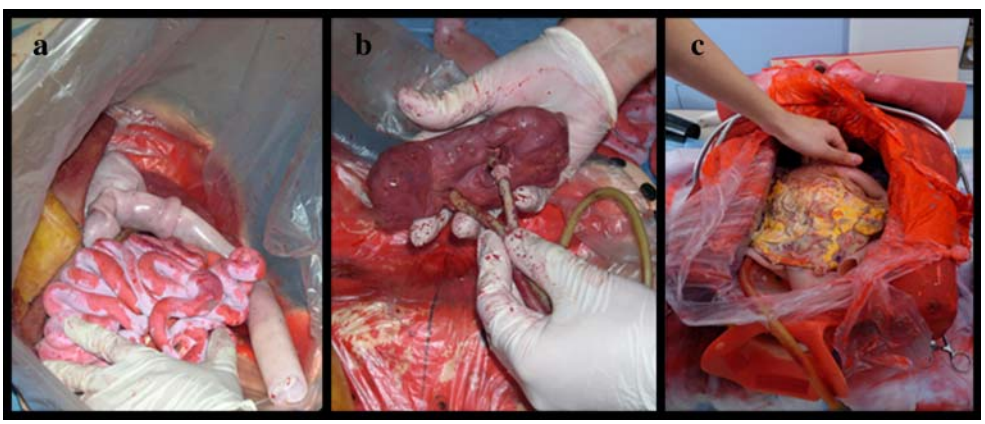

Figure 9 **a** Simulated bowel, **b** spleen with vasculature, **c** completed model ready for simulation. Developed by Noel Irias, SASC, 2006.

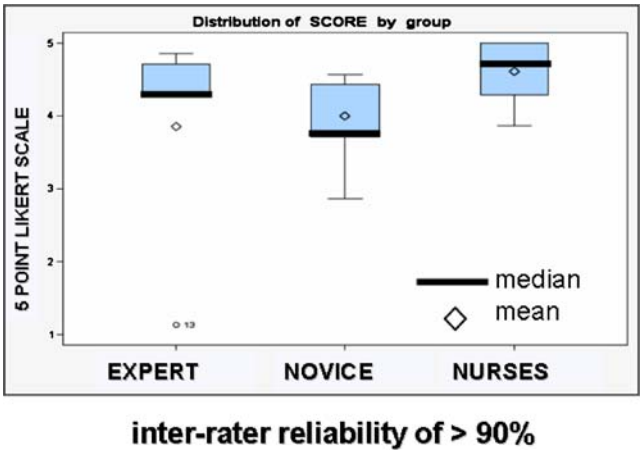

Figure 10 Face validity scored on 5-point Likert scale.

As depicted in Fig. 10, novice and expert surgeons gave median scores of 4.29 and 4.43, respectively, for face validity compared to the scrub nurses who deemed face validity to be higher at 4.71, although not significantly different. The interrater reliability for face validity questions was high, indicating good agreement between raters. Further, the majority of experts (80%) considered the simulation suitable for initial training in general surgery, thus establishing its content validity. To establish construct validity, the technical and nontechnical performances of novice and expert laparoscopic surgeons were evaluated throughout a simulated intra-abdominal hemorrhage during a laparoscopic cholecystectomy. In assessment of nontechnical skills, experts scored significantly higher, 89.7%±5.9, than novices, 51.3%±14.9 ($P<0.001$). Although technical skill assessment measured no difference in Veress safety and laparoscopic equipment setup skills between groups, there was a significant overall difference between the two groups in their ability to identify bleeding and identify hemodynamic instability. Further, the experts demonstrated a superior ability to convert to an open laparotomy and control the intra-abdominal hemorrhage encountered. Interestingly, while most surgeons chose the correct incision to open the abdomen, some of the novice participants did not perform a laparotomy despite the hemodynamic instability of the patient, thus leading to compromise of the patient. Overall, the protocol was able to discriminate well between the technical and nontechnical performance of novices vs experts (see Fig. 11).

In the USA, several organizations have been collaborating to ensure that simulation continues to integrate into the daily training of general surgeons. The Residency Review Committee of Accreditation Council for Graduate Medical Education has mandated that all general surgery residencies must have a skills training facility or access to one by 2008. In an effort to provide guidance to residency programs, the American College of Surgeons has established specific criteria for training, curriculum, personnel, and resources. Further, they created an accreditation process recognizing centers: level 1 (Comprehensive Education Institute) and level 2 (Basic Education Institute; see http://www.facs.org/education/ accreditationprogram/list.html).

The Simulation and Skills Center (SASC) at BIDMC is an ACS level 1 Education Institute (see http://www.BIDMC.Harvard.edu/SASC). We provide comprehensive programs for many learners to include physicians, nurses, residents, medical students, and allied health professionals. Programs are available for cognitive and psychomotor skills training as well as comprehensive team training in a mock OR as well as a critical care area. Additionally, the SASC serves as a regional testing facility for the SAGES FLS program.

The General Surgery residents have an annual curriculum with 2 h of protected time in the SASC each week. Many of the skills overlap with the anticipated ACS-APSD

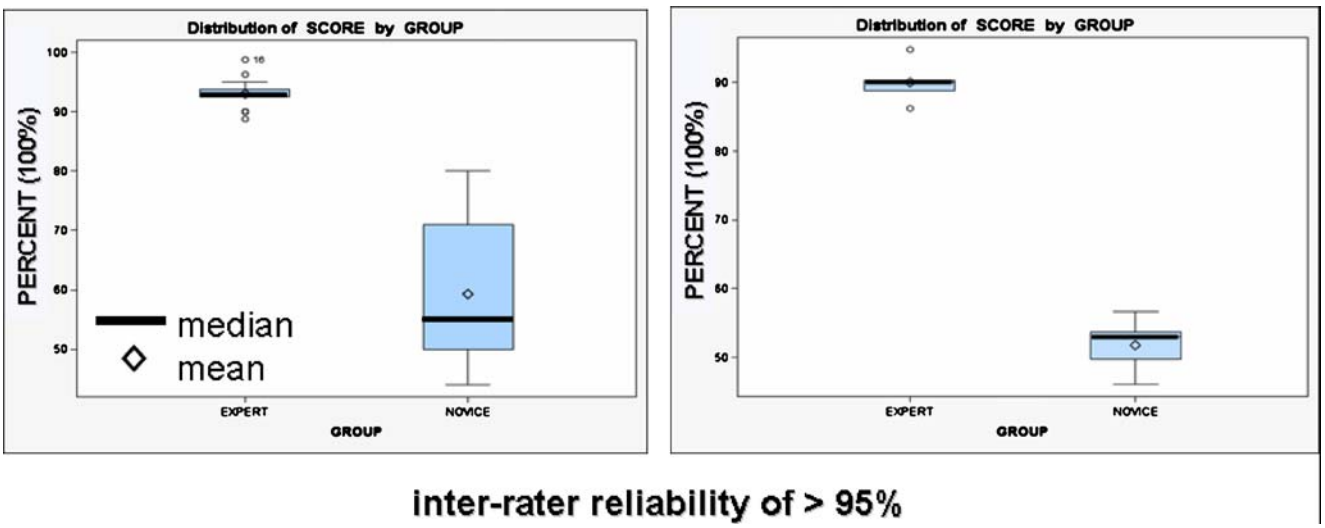

Figure 11 Total technical and nontechnical skills assessment scores.

curriculum ranging from laparoscopic knot tying to chest-tube placement. Interns are required to pass the basic endoscopic surgery test (BEST) for successful promotion to PGY2 year. Tasks are modified from Top Gun. By the PGY4 level, residents must pass the FLS examination prior to becoming a Chief Resident.

In 2007, we extended FLS expectation to faculty and community surgeons. As of this year, BIDMC and Cambridge Hospital, Boston, MA has requested FLS certification as the criteria for laparoscopic privileges for all general surgeons. Furthermore, the Harvard malpractice carrier, CRICO, has announced US$500 premium rebate for all surgeons who demonstrate a FLS certificate. As a patient-safety initiative, the CRICO rebate for FLS certification has been supported by BIDMC, Brigham and Women's, and Mass General Hospital.

In the future, surgeons will likely train and be assessed in the mock OR environment, especially as more ACS Education Institutes make mock ORs more commonplace and geographically assessable. At BIDMC, we have challenged surgeons in practice age 50 to 83 years of age with laparoscopic cholecystectomy crisis scenarios. After each scenario, the surgeon is debriefed while reviewing the videotape. Doing cases in a simulated OR will likely replace oral Board Exams in a crowded hotel room and may be used for maintenance of certification purposes.

Overcoming financial obstacles may further adoption of simulation. US government agencies like the Agency for Healthcare Research and Quality (AHRQ) the medical safety proponent of the US Department of Health and Human Services (HHS) and the US Army's Telemedicine and Advanced Technology Research Center (TATRC) represent major sources of funding for research and development in medical simulation. For example since 1997, TATRC has funded 44 projects totaling US$12,555,000 in funding and by 2007 expects to fund a total of 174 projects totaling US$74,811,000 (see http://www.medsim.org/articles/AIMS_2004_Report_Simulation-based_Medical_Training.pdf). AHRQ recently awarded more than US$5 million in fiscal year 2006 for medical simulation research as part of its effort to improve patient safety.

Other efforts seek to mandate via Congressional legislation that medical simulation become the standard for health care professional training in the US. The Advanced Initiatives in Medical Simulation (http://www.medsim.org/), a coalition of key individuals and industries, has proposed Congressional legislation known as the "Simulation Act of 2007." This proposed legislation would have four provisions: (1) authorizing grants to health professional schools through the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health (NIH) and the AHRQ to fund advanced medical simulation research; (2) authorizing grants through NIBIB and AHRQ for health professional schools to purchase simulation technology and equipment for training purposes; (3) creating Centers of Excellence to conduct medical simulation research into enhancing and expanding the utilization of relevant technologies and simulation-based skills training for health professional schools; and (4) establishing a federal advisory board for medical simulation.

Simulation technology can improve surgical residency training and better assure competency. Surgeons will no longer be solely judged based on subjective measures of experience but rather will be assessed objectively by proficiency-based tools such as the FLS examination. As VR technology evolves and becomes more cost-efficient, simulator technology will play an increasing role in the training and certification of general surgeons before embarking on new procedures and emerging technology. Totally simulated OR environments will likely be used to assess professional skills like leadership, crisis management, and communication in preparing resident surgeons for clinical practice. The ACS Education Institutes will undoubtedly serve as a resource for maintenance of certification of surgeons already in practice. Through simulation training, surgeons will demonstrate our commitment to our patients to reduce surgical error and improve safety.

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Risk of Malignancy in Resected Cystic Tumors of the Pancreas ≤3 cm in Size: Is it Safe to Observe Asymptomatic Patients? A Multi-institutional Report

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Abstract Recent international consensus guidelines propose that cystic pancreatic tumors less than 3 cm in size in asymptomatic patients with no radiographic features concerning for malignancy are safe to observe; however, there is little published data to support this recommendation. The purpose of this study was to determine the prevalence of malignancy in this group of patients using pancreatic resection databases from five high-volume pancreatic centers to assess the appropriateness of these guidelines. All pancreatic resections performed for cystic neoplasms ≤3 cm in size were evaluated over the time period of 1998–2006. One hundred sixty-six cases were identified, and the clinical, radiographic, and pathological data were reviewed. The correlation with age, gender, and symptoms (abdominal pain, nausea and vomiting, jaundice, presence of pancreatitis, unexplained weight loss, and anorexia), radiographic features suggestive of malignancy by either computed tomography, magnetic resonance imaging, or endoscopic ultrasound (presence of solid component, lymphadenopathy, or dilated main pancreatic duct or common bile duct), and the presence of malignancy was assessed using univariate and multivariate analysis. Among the 166 pancreatic resections for cystic pancreatic tumors ≤3 cm, 135 cases were benign [38 serous cystadenomas, 35 mucinous cystic neoplasms, 60 intraductal papillary mucinous neoplasms (IPMN), 1 cystic papillary tumor, and 1 cystic islet cell tumor], whereas 31 cases were malignant (14 mucinous cystic adenocarcinomas and 13 invasive carcinomas and 4 in situ carcinomas arising in the setting of IPMN). A greater incidence of cystic neoplasms was seen in female patients (99/166, 60%). Gender was a predictor of malignant pathology, with male patients having a higher incidence of malignancy (19/67, 28%) compared to female patients (12/99, 12%; $p<0.02$). Older age was associated with malignancy (mean age 67 years in patients with malignant disease vs 62 years in patients with benign lesions ($p<0.05$). A majority of the patients with malignancy were symptomatic (28/31, 90%). Symptoms that correlated with malignancy included jaundice ($p<0.001$), weight loss ($p<0.003$), and anorexia ($p<0.05$). Radiographic

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features that correlated with malignancy were presence of a solid component ($p<0.0001$), main pancreatic duct dilation ($p=0.002$), common bile duct dilation ($p<0.001$), and lymphadenopathy ($p<0.002$). Twenty-seven of 31(87%) patients with malignant lesions had at least one radiographic feature concerning for malignancy. Forty-five patients (27%) were identified as having asymptomatic cystic neoplasms. All but three (6.6%) of the patients in this group had benign disease. Of the patients that had no symptoms and no radiographic features, 1 out of 30 (3.3%) had malignancy (carcinoma in situ arising in a side branch IPMN). Malignancy in cystic neoplasms ≤3 cm in size was associated with older age, male gender, presence of symptoms (jaundice, weight loss, and anorexia), and presence of concerning radiographic features (solid component, main pancreatic duct dilation, common bile duct dilation, and lymphadenopathy). Among asymptomatic patients that displayed no discernable radiographic features suggestive of malignancy who underwent resection, the incidence of occult malignancy was 3.3%. This study suggests that a group of patients with small cystic pancreatic neoplasms who have low risk of malignancy can be identified, and selective resection of these lesions may be appropriate.

Keywords Cystic pancreatic neoplasms · Serous cystic neoplasm · Mucinous cystic neoplasm · Intraductal papillary mucinous neoplasm · Selective resection

Introduction

Advancements in high resolution abdominal imaging and its widespread use have led to the increasing discovery of incidental, asymptomatic cystic lesions in the pancreas. Depending on the type, cystic pancreatic neoplasms have varying malignant potential. The benign cystic tumors of the pancreas consist of the serous cystic neoplasms (SCN), which are the most common, and the rare cystic papillary tumor types. Mucin-producing cystic tumors of the pancreas, which consist of intraductal papillary mucinous neoplasms (IPMN) and mucinous cystadenomas (MCN), are generally considered premalignant. Depending on the type of tumor, the prevalence of carcinoma associated with mucin-producing cystic neoplasms is widely varied among surgical resection series in the literature ranging from 6% to as high as 60%.[1–11] Although smaller tumor size is associated with a lower risk of malignancy with the lesion, upon review of literature, the natural history of mucinous lesions over time is not well characterized. Because of the uncertainty of malignant risk in the incidentally discovered cystic neoplasm, the patient presenting with a small (≤3 cm) asymptomatic tumor represents both a challenging diagnostic and management dilemma.

Unfortunately, current methods of evaluating cystic pancreatic lesions are limited in differentiating pseudocyts from cystic tumors. More importantly, preoperative imaging or endoscopic studies do not reliably differentiate between serous and mucinous neoplasms. The imaging features of serous and mucinous neoplasms can overlap considerably.[12,13] Although the use of endoscopic ultrasound (EUS) and analysis of the cystic fluid can generally differentiate between the two types, accuracy of no greater than 80% is reported in the literature.[13,14] Even more difficult is determining the presence of malignancy in the subgroup of mucinous neoplasms due to the lack of cellularity in the aspirate. As such, some argue for routine resection of all cystic lesions of the pancreas for all medically fit patients due to the uncertainty of diagnostic screening and potential malignant risk.[15,16] It remains to be determined if such an aggressive approach should be recommended for all these patients, many of whom may have benign disease who are subjected to a major pancreatic resection with an associated morbidity, which may be as high as 58% and mortality rate of 2–4%, even in high volume centers.[9,16,17,21] Currently, the international consensus guidelines for the management of mucinous cystic neoplasms (MCN) suggests selective management with close follow-up of patients with cystic tumors less than 3 cm in size who are asymptomatic and with no concerning features suggestive of malignancy on imaging, namely, mural nodules, main pancreatic duct dilation, common bile duct dilation, or adenopathy.[2] However, there is limited published data to support or refute the recommendations proposed by the consensus guidelines. The purpose of this study was to test the appropriateness of these guidelines (Table 1), to identify factors associated with malignancy in these small cystic tumors, and to determine the prevalence of malignancy in the group of patients who had asymptomatic, small ≤3 cm cystic neoplasms. In this study, we surveyed all patients who underwent pancreatic resection for cystic neoplasms ≤3 cm at five high-volume pancreatic surgery centers over an 8-year period. We report the results of this analysis, with a particular focus on asymptomatic patients with no concerning radiographic features of malignancy to determine the prevalence of occult malignancy in this subgroup of patients.

Table 1 Characteristics of Pancreatic Cystic Neoplasms with Low Risk of Malignancy as Described in the Published International Guidelines[a]

Characteristics
Asymptomatic
Size <30 mm
Main Pancreatic Duct Dilation <6 mm
No solid component within or associated with cyst on imaging

[a] [2]: p. 28

Materials and Methods

An Institutional Review Board (IRB)-approved retrospective review of all pancreatic resections for cystic neoplasms over the time period of 1998–2006 was performed at five high-volume pancreatic surgery centers (University of Michigan Medical Center, UCLA Medical Center, University of Pennsylvania Medical Center, Vanderbilt Medical Center, and University of Virginia Medical Center). Clinical, radiographic, surgical, and pathology records of patients were analyzed, who had a diagnosis of a cystic neoplasm measured on post-resection pathology to be ≤3 cm. All patients underwent radiographic imaging including computed tomography (CT), magnetic resonance imaging (MRI), or EUS. A cystic lesion was considered symptomatic if preoperative evaluation and subsequent diagnostic imaging was performed for gastrointestinal (GI)-related complaints, such as abdominal pain, nausea or vomiting, and weight loss, and asymptomatic if it was discovered incidentally by imaging. Lesions were considered to be malignant when carcinoma in situ or invasive cancer was present. Factors analyzed for their correlation with malignancy included age, gender, and the following symptoms: abdominal pain, nausea and vomiting, jaundice, history of pancreatitis, unexplained weight loss, anorexia, and diarrhea. Preoperative imaging features that were deemed suggestive of malignancy included solid component associated with or present within the cystic neoplasm, dilated common bile duct, dilated main pancreatic duct, lymphadenopathy, multiple septae, and calcifications.

Statistical Analysis

Standard univariable analyses were used to determine the correlation with malignancy. Comparisons were made using a Fisher's exact test or chi-squared test for nominal variables (positive symptoms, radiographic signs, etc) and a Student's *t* test for continuous variables (age). A univariate analysis was performed to identify risk factors for malignancy using logistic regression analysis. To evaluate for independent predictors of malignancy, a multivariate analysis was performed with a model using factors identified as being significant in the univariate or those with a *p* value of less than 0.20. A *p* value of less than 0.05 was considered statistically significant. Results are presented as mean±standard deviation.

Results

Demographics

At total of 166 pancreatic resections of cystic pancreatic neoplasms ≤3 cm were performed at five high-volume pancreatic surgical centers over the period of 1998–2006. The mean age of these patients at the time of diagnosis was 63 years (range, 22–89 years). The cohort was comprised predominantly of female patients (99/166, 60%). Malignancy was present in 31 (19%) patients. The age and gender distribution of patients diagnosed with benign lesions and those found to have malignant lesions are listed in Table 2. Older age was significantly associated with malignancy; patients with benign neoplasms had mean age 62.3±12.4 years, and patients with malignant neoplasms had mean age of 66.9±9.9 years ($p<0.05$). Regardless of the type of tumor, there was a greater prevalence of cystic neoplasms in the female population. The majority of patients with SCN were female (30/38, 79%), whereas 53% (26/49) of MCN, and 55% (42/77) of IPMN were found in female patients. Similarly, 42 of 77 IPMNs (55%) were found in female patients. Although the majority of

Table 2 Comparison of Age and Gender between Patients with Benign and Malignant Tumors

Factors	Patients with Benign Tumors (n=135)	Patient with Malignant Tumors (n=31)	p value
Age	62.3±12.4* yrs	66.9±9.9 years[a]	<0.05
Male	48	19(28%)[b]	<0.02[c]
Histopathology			
Serous cystic neoplasms	8	0	
Mucinous cystic neoplasms	15	8 (35%)[b]	NS (=0.5)[c]
IPMN	24	11(31%)[b]	NS(<0.09)[c]
Cystic islet tumor	1	0	
Female	87	12(12%)[b]	
Histopathology			
Serous cystic neoplasms	30	0	
Mucinous cystic neoplasms	20	6(23%)	
IPMN	36		
Cystic papillary tumor	1	0	

[a] Calculated mean age±standard deviation
[b] Indicates percent incidence within the same gender group
[c] Comparison of the incidence of malignancy between male and female patients

patients with cystic neoplasms were women (n=99, 60%), there was a significant (p<0.02) association of male sex with malignant neoplasms; 19/31 (61%) invasive cancers were found in men, indicating a 28% prevalence (19/67 men) compared to 12% prevalence (12/99) in female patients.

Clinical Presentation

One hundred twenty one of 166 patients had one or more symptoms indicative of upper abdominal pathology including abdominal pain, jaundice, pancreatitis, weight loss, nausea and vomiting, anorexia, and diarrhea at the time of his or her diagnosis. Forty-five of 166 patients were asymptomatic and had incidental discovery of their cystic neoplasm during imaging for another reason. The association between these six symptoms and malignancy was assessed.

There was a significant relationship with having one or more symptoms and the risk of malignancy, as 28 of 121 symptomatic patients (23%) had invasive cancer, whereas only 3 of 45 asymptomatic patients (6.6%) had invasive cancer (p<0.01). A detailed comparison of symptoms between patients with benign and malignant lesions is shown in Table 3, with jaundice (p<0.001), weight loss (p< 0.003), and anorexia (p<0.05) showing significant association with malignant cystic lesions. Overall, abdominal pain was the most common presenting symptom between the two groups of patients with 76/166 (57%) in the benign group and 17/31 (55%) in the malignant group, but there was not a significant association with this factor and malignancy as neither was having a history of pancreatitis, nausea and vomiting, or diarrhea.

Radiographic Data

The most common preoperative imaging utilized was CT with all but six patients having the study (160/166, 96%), followed by EUS in 99/166 patients (60%), and MRI in 29/166 patients (17%). To determine the relationship between radiographic and/or endoscopic features and the risk of malignancy in patients who underwent resection, we assessed the presence or absence of the following features based on radiographic or endoscopic imaging: presence of a solid component within or associated with the cyst, main pancreatic duct dilation, common bile duct dilation, lymphadenopathy, presence of septae, and calcifications (Table 4). Overall, 69 of the 166 patients (42%) had at least one of these concerning radiographic features. A significantly higher percentage of patients with malignant lesions (p<0.05) had at least one radiographic feature; 27 of 31 patients (87%) with malignant lesions vs 42 of 135 (31%) with benign lesions. Radiographic features that had significant association with malignancy included presence of a solid component (p<0.0001), main pancreatic duct dilation (p=0.002), common bile duct dilation (p<0.001), and lymphadenopathy (p<0.001). The presence of calcifications and septae was not significantly associated with malignancy, although it has been reported in other series to be significant determinants of malignant tumor type.[22,26]

When examining asymptomatic patients, 15 of 45 (33%) patients had radiographic features for malignancy, whereas 30 of the 45 asymptomatic patients (66%) had no discernable features suggestive of malignancy preoperatively by CT, MRI, or EUS prior to cyst fluid analysis. When we discriminated asymptomatic patients for those who had no concerning radiographic features, there was 1 (3.3%) patient out of 30 who harbored malignancy; a branch-duct IPMN carcinoma in situ found to be malignant preoperatively by fine needle aspiration (FNA) and cytology.

About 99 of 166 patients underwent EUS, and 77 of the 99 patients (71%) had concurrent FNA with cytologic analysis of the lesion at the time of their examination. Twenty patients had suspicious findings for malignancy with presence of atypical glandular or atypical epithelial cells in the cyst fluid after cytologic analysis. About 19 of the 70 patients (27%) were confirmed to have malignancy after resection; however, only 15 of those patients that had preoperative cytology findings worrisome for malignancy ultimately had diagnosis of invasive cancer. EUS with FNA analysis of cyst fluid cytology resulted in four false

Table 3 Clinical Presentation of Patients with Cystic Pancreatic Neoplasms ≤3 cm

Symptoms	Patients with Benign Tumors (n=135)	Patient with Malignant Tumors (n=31)	p value
Symptomatic	93	28	<0.01
Asymptomatic	42	3	<0.01
Abdominal pain	76(57%)	17(55%)	NS
Jaundice	9(7%)	10(32%)	.0002
Pancreatitis	21(16%)	7(23%)	NS
Weight loss	11(8%)	11(35%)	.0002
Nausea/vomiting	13(10%)	5(16%)	NS
Anorexia	2(1.5%)	3(10%)	.035
Diarrhea	3(2%)	2(6%)	NS

Table 4 Comparison of Radiographic Features Between Patients with Benign and Malignant Tumors

Radiographic Feature	Patients with Benign Tumors (n=135)	Patient with Malignant Tumors (n=31)	p value
≥1 Radiographic feature	42	27	<0.05
Mo radiographic feature	93	4	<0.05
Solid component	4 (3%)	15 (48%)	<0.0001
Main pancreatic duct Dilation	21 (16%)	13 (43%)	0.0001
Common bile duct dilation	6 (6%)	11 (39%)	<0.0001
Adenopathy	5 (4%)	7 (23%)	<0.002
Calcifications	2 (1.5%)	1 (3%)	NS
Presence of septae	25 (19%)	3 (13%)	NS

negative and five false positive findings. Based on this data, the sensitivity and specificity of EUS with FNA and cytologic analysis to diagnose a malignant lesion were 79 and 90%, respectively.

A recent report from the Cooperative Pancreatic Cyst Study has shown that cyst fluid carcinoembryonic antigen (CEA) concentration >192 ng/ml has an accuracy of 79% in differentiating mucin-producing and non-mucinous lesions.[13] In our study, cyst fluid CEA levels were available in 20 of the 99 patients who underwent EUS. Six out of 11 (54.5%) mucin-producing tumors (IPMN+MCN) showed elevated cyst fluid CEA levels >192 ng/ml. One out of nine non-mucin producing tumors (SCN) had elevated CEA >192 ng/ml. The mean CEA levels between mucinous and non-mucinous neoplasms were significantly different; the mean CEA level in non-mucinous neoplasms measured 53.6±81.8 ng/ml, whereas the mean CEA level in mucin-producing neoplasms measured higher at 1,141.9±1,837.7 (p<0.03). Overall, elevated cyst fluid CEA concentration at a cutoff point of >192 ng/ml was found to confer a sensitivity of 55% and specificity of 89% for separating mucinous from non-mucinous lesions. There were three mucin-producing neoplasms identified by elevated cyst fluid CEA levels that were ultimately confirmed to have malignancy after resection. There was a higher trend in the mean CEA levels in the cyst fluid of malignant mucin-producing lesions (1,999.1± 2,645.1) compared to benign mucin-producing lesions (937.19±1,632.4); however, the results are limited by sample size.

Surgical Data

Of types of pancreatic resections that were performed to remove cystic lesions ≤3 cm in this report, the most common operation performed was pancreaticoduodenectomy (88/166, 54%). Distal pancreatectomy was performed in 64/166 (38%) patients. Other resection procedures, ranging from subtotal to total pancreatectomy, were performed in 14/166 (8%) patients. Interestingly, a significantly higher proportion of patients who had malignant lesions underwent pancreaticoduodenectomies compared to other modes of resection. About 27 of 31 patients (87%) with malignant lesions underwent pancreaticoduodenectomies, whereas only 4 of 31 patients (13%) underwent distal pancreatectomies. When looking at asymptomatic patients with no concerning radiographic features, most of the lesions were found in the body or tail of the pancreas, as the predominant mode of resection was a distal pancreatectomy (n=19, 63%). Eight patients in this group underwent pancreaticoduodenectomy, including one patient who was determined to harbor a malignant IPMN.

Pathology Data

Table 5 outlines the final histopathologic diagnosis and distribution of tumors from the 166 cases. The majority of the small cystic pancreatic lesions were mucinous; (126/166, 76%). The most common type of tumor was IMPN, accounting for 77/166 (46%) of all lesions. Depending on the neoplasm's communication with the pancreatic ductal system, the IPMNs were further classified into the main duct (n=67) type and side-branch type (n=10). Malignant tumors were found in 17 (22%) of the 77 IPMNs; 3 out of 10 side-branch IPMNs (30%) and 14 of 67 main branch IPMNs (21%) have malignant tumors ranging from carcinoma in situ to invasive cancer. The next most common cystic lesion was MCN with 49/166 (30%)

Table 5 Type and Distribution of 166 Cystic Tumors ≤3 cm

Tumor Histopathology	Benign Tumors (n=135)	Malignant Tumors (n=31)
Scrous cystic Neoplasms	38	0 (0)
Mucinous cystic Neoplasms	35	14 (29%)[a]
IPMN (main branch)	53	14 (21%)*
JPMN (silt branch)	7	3 (30%)*
Cystic papillary tumor	1	0 (0)
Cystic islet tumor	1	0 (0)

[a] Percentage based upon tumors of same histopathology

patients having the diagnosis. About 14 of the 49 patients (29%) with MCN had invasive mucinous cystadenocarcinomas. There were 38/166 (23%) cases of SCN, which were all benign. One patient (0.6%) had a cystic papillary tumor, and one patient (0.6%) had another rare lesion, a cystic islet tumor.

Of the 45 asymptomatic patients, 3 (6.6%) had malignant tumors, 2 invasive main-duct IPMNs, and 1 side-branch IPMN carcinoma in situ. The distribution of tumors in the group of asymptomatic patients with no concerning features of malignancy followed that of the overall group of patients in the study, with bulk of the tumor types being mucin-producing IPMNs and MCNs at 14/30(47%) and 9/30(30%), respectively.

Univariate and Multivariate Analysis of Risk Factors

Significant factors that correlated with malignancy from our univariate analysis are summarized in Table 6. These factors were then used to construct a multivariate regression model. The results of the analysis are displayed in Table 7. Three independent predictive factors of malignancy were found: the clinical symptom of weight loss and the radiographic features of a solid component associated with the tumor and common bile duct dilation. The dominant risk factor predictive of malignancy was the presence of a solid component associated with the cystic tumor ($p<0.0001$).

Discussion

To validate the guidelines proposed by the international consensus report on the management of cystic neoplasms of the pancreas, we analyzed the pancreatic resection database of five high-volume pancreatic centers and assessed pathologic diagnosis as a function of size, presence or absence of symptoms, and presence or absence of specific imaging features. Several studies correlating size and malignancy risk have revealed that smaller cystic neoplasms are less likely to be malignant. In our study, 31 of 166 (19%) patients with cystic pancreatic neoplasms <3 cm had malignant lesions, which is in accordance with the results of other series that report malignancy rates ranging between 13–20% in small lesions.[3,9,22,23,25] Our data shares the inherent limitations of previous studies, which most certainly overestimate the overall risk of malignancy in small lesions, as it is quite likely that experienced clinicians selected those patients for surgical intervention at highest risk. However, whereas the focus of our investigation was those patients without risk factors or symptoms, to validate the recommendations of current guidelines, it is likely that we overestimate the risk in that population as well.

In our study, the majority, 126 (76%) of 166 small cystic pancreatic tumors, were of the mucin-producing types. As expected, there was negligible malignancy risk in non-mucin producing neoplasms, as all malignant tumors occurred in the setting of MCN or IPMN. It has been suggested that IPMN arising in the side ducts are less aggressive than the main duct;[2,23] however, we did not note a significant ($p=0.68$) difference in the incidence of malignancy between side-branch and main-duct IPMNs in the report. This may be limited by the sample size.

The mean age of patients who underwent surgical resection for pancreatic cystic lesions ≤3 cm was 63± 12 years. Other studies have shown cystic neoplasms to occur mostly in patients of the fifth and sixth decades of life.[1,2,6,8,11,20,23] Also consistent with other reports, we observed that older age (>67 years in this study) was associated with malignant pathology. Recently, Spinelli et al.[8] showed in their series that age greater than 70 years was strongly associated with malignancy. Multiple other

Table 6 Summary of Factors Correlating with Malignancy

Risk Factor	OR	95% CI	*p* value
Age >67	1.888	(0.999–3.076)	0.0495
Gender (Male)	2.870	(1.284–6.413)	0.0102
Jaundice	6.667	(2.423–18.345)	0.0002
Pancreatitis	1.583	(0.605–4.144)	0.3492
Weight Loss	6.200	(2.374–16.193)	0.0002
Nausea/Vomiting	1.805	(0.592–5.504)	0.2993
Anorexia	7.125	(1.137–44.648)	0.0360
Diarrhea	2.259	(0.395–12.927)	0.3600
Pain	0.943	(0.430–2.067)	0.8828
Solid Component	30.703	(9.073–103.902)	<0.0001
Dilated CED	11. 825	(3.933–35.549)	<0.0001
Dilated MPD	5.353	(2.256–12.702)	0.0001
Adenopathy	7.583	(2.222–25.852)	0.0012
Calcifications	2.217	(0.195–25.259)	0.5214
Septae	0.550	(0.154–1.970)	0.3587

OR Odds ratio; *CI* Confidence interval

Table 7 Multivariate Analysis of Significant Factors Associated with Malignancy

Risk Factor	OR	95% CI	*p* value
Age >67	1.159	(0.349–3.855)	0.8092
Gender (male)	3.343	(0.879–12.709)	0.0765
Jaundice	1.926	(0.311–11.935)	0.4811
Weight loss	6.062	(1.333–27.5 71)	0.0197
Anorexia	0.758	(0.040–14.220)	0.8528
Solid component	65.647	(12.409–347.291)	<0.0001
Dilated CUD	9.550	(1.775–51.381)	0.0086
Dilated MPD	1.529	(0.369–6.331)	0.5581
Adenopathy	6.813	(0.969–47.898)	0.0538

OR Odds ratio; *CI* Confidence interval

reports have noted an increased incidence of malignant disease occurring at a median age of 65 to 70 years in both MCNs and IPMNs.[6,11,20,23]

Regardless of tumor type, the majority of cystic neoplasms in our study occurred in women. Prevalence of cystic neoplasms in female patients has been observed in other studies as well.[3,4,5,11,19] The overall incidence of malignancy was significantly higher in men, 14 (28%) of 67, compared to women 12(12%) of 99 ($p<0.02$). When analyzing individual tumor types, the overall trend of higher malignant tumors in the male population was observed; 35% of men with MCN having malignant tumors vs 23% women, and 31% of men with IPMN having invasive disease vs 14% of women. Recent studies from Johns Hopkins and the Mayo Clinic also showed that male gender was strongly associated with malignancy risk in patients with IPMN.[7,24]

The presence of one or more symptoms was a significant predictor of malignant pathology. Taken individually, symptoms of jaundice, weight loss, and anorexia had statistically significant associations with malignant tumors (Table 3). Weight loss, moreover, was found to be an independent risk factor when considered in a multivariate analysis (Table 7). Multiple observations have been made in literature with regards to symptoms and association with malignancy. In a recent study by Moesinger et al.,[20] less than 50% of the patients with SCNs and benign MCNs had symptoms, where more than 80% of their patients with invasive disease had symptoms. We observed that 28 out of 31 (90%) patients with invasive tumors had symptoms on presentation. Previous reports have not shown that anorexia correlated with malignancy, as it was observed in this study. Jaundice and weight loss, however, have been shown in other series to suggest malignant risk.[21]

As imaging technology has evolved, radiographic characterization of cystic pancreatic lesions has allowed correlation of distinct cyst features with malignant risk. Multiple studies have reported the presence of solid components within the cyst or associated with the cyst to be a significant radiographic feature predictive of malignancy.[2,9,22,25] Other studies have shown pancreatic duct dilation (especially in IPMN), common bile duct dilation, adenopathy, septae, and calcifications to be suggestive of malignant processes.[21,22] In our report, the most significant radiographic feature associated with malignancy in univariate analysis was the presence of a solid component ($p<0.0001$) followed by common bile duct dilation ($p<0.001$), pancreatic duct dilation ($p=0.002$), and lymphadenopathy ($p<0.002$). Both the presence of a solid component and common bile duct dilation were found to be independent predictors when considered in a multivariate regression model (Table 7).

Using radiographic features alone has limited sensitivity in differentiating mucinous from serous neoplasms and cannot accurately determine malignancy especially in small cystic lesions.[12] An added advantage of EUS imaging is the ability of the physician to obtain cyst fluid analysis. In the Cooperative Pancreatic Cyst Study, EUS with cyst fluid analysis for elevated CEA (>192 ng/ml) was seen to accurately determine mucin-producing lesions in 79% of cases.[13] In our analysis, the ability of this test to separate mucin-producing lesions from non-mucinous lesions had sensitivity of 55% and specificity of 89%. We also examined the utility of preoperative cyst fluid cytologic analysis to determine malignancy by presence of atypical cells. The sensitivity and specificity of diagnosing a malignant cystic lesion by cyst fluid cytology was 79 and 90%, respectively. This is consistent with other reports that have shown sensitivity and specificity of cytologic analysis to be around 70–80%.[3,13]

The management of an asymptomatic patient that presents with no discernable radiographic or endoscopic features of malignancy lies at the heart of the controversy regarding management of cystic pancreatic neoplasms. The data from our study suggests that, based on significant predictive factors of malignancy, asymptomatic patients with small cystic pancreatic neoplasms have a very low malignant potential. Among asymptomatic patients that had no radiographic features for malignancy that underwent surgical resection, only 1 patient in 30 (3.3%) was found to harbor an occult malignancy. This patient who had no radiographic features in his incidentally discovered lesion was a 60-year-old male with prior history of hepatitis B who presented with vague complaints of fatigue. An abdominal ultrasound revealed a hypoechoic mass in the head of the pancreas, and subsequent work up with CT, MRI, and EUS revealed no distinctive features in this 1-cm cystic lesion. FNA performed at the time of the EUS ultimately revealed rare groups of atypical glandular cells, suspicious for adenocarcinoma. After pancreaticoduodenectomy, the patient's final diagnosis was a 1.5-cm side-branch IPMN carcinoma in situ.

When considering the management plan of patients with cystic tumors ≤3 cm in size, the risk of occult malignancy in the asymptomatic patient with no concerning radiographic features must be weighed against the morbidity and mortality rates associated with pancreatic resection. We observed a 3.3% risk of occult malignancy in this cohort of patients who underwent surgical resection for their incidentally discovered cystic neoplasms, a rate comparable to operative mortality rates for pancreatic resection reported at many centers, including high-volume centers in the USA.[17] As noted above, given the inherent bias of our study, this likely represents an overestimate of the risk in such patients, which provides reassurance for a conservative

approach in this cohort. In several other reports, incidentally discovered cystic neoplasms that were small had malignancy risks comparable to operative mortality rates. In the study by Allen et al.,[9] the authors concluded that patients with cystic lesions less than 3 cm in diameter and without a solid component to the lesion had a malignancy risk of 3% comparable to the operative risk of pancreatectomy of 2% in high volume centers. Even in the study by Hardacre et al.,[16] which argues for resection of all cystic pancreatic neoplasms, the incidence of malignancy was only 4.5% in asymptomatic lesions (the authors did not differentiate lesions by size). The operative mortality rate in that series was 3.3% and the operative morbidity rate was 58%. Adding the benefit of EUS with FNA and cytologic assessment, all patients in our study that had malignant tumors were appropriately selected for resection preoperatively.

There is convincing data in the literature to support initial non-operative approach in asymptomatic patients with tumors bearing no concerning radiographic features. In a large series by Walsh et al.,[18] 161 asymptomatic patients with small cysts were followed radiographically over a median time period of 24 months. None of the patients who underwent delayed resection was found to have malignancy. Similarly in the study by Allen et al.,[9] 369 patients were selected for non-operative management based on small size, no symptoms, and no solid component radiographically. After a median follow-up of 2 years, 29(8%) patients developed changes resulting in resection. Only eight (2%) patients with invasive cancer were identified in the group that underwent radiographic surveillance.

The diagnosis and management of cystic pancreatic neoplasms are becoming refined as more and more series elucidate predictive factors of malignancy. However, it is clear that a better understanding of the natural history of cystic pancreatic neoplasms need to occur based on long-term data acquired from prospective databases. Based on retrospective analysis, this multi-institutional review of resection data of small cystic neoplasms from five high-volume centers suggests that a group of patients with a low risk of malignancy can be identified and be safely followed in accordance with the current consensus guidelines.

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Discussion

Jennifer F. Tseng, M.D. (Worcester, MA): I want to congratulate Dr. Lee, Dr. Simeone, and colleagues from five institutions for their work putting together a multi-institution series on cystic tumors. Dr. Lee, thank you for an excellent presentation and for allowing me to review the manuscript. I have two questions and a comment.

First, in contrast to the existing literature, you found in your series that side-branch IPMNs did not have a decreased risk of malignancy compared with main duct variants. Why do you think this is, and do you think it reflects the heterogeneous nature of your series?

Second, it is interesting that more men than women have malignancy at OR, Dr. Fernandez and I found in our series on serous cystadenomas that men had larger lesions and also presented at a later age, suggesting a delay in diagnosis. Do you think this is at play in your series; were men older?

The final question is your manuscript refers to the role of EUS. How did you define the sensitivity and specificity and accuracy of the cytology? Was it the pathologist calling it malignant? Were biopsies that had no epithelium present and thus were not diagnostic of malignancy termed benign or indeterminant, and how was the presence of mucin considered in the determination for operation? Do size and symptoms now trump mucin in your view in terms of a determination of whether this patient needs to go to the OR?

And finally my comment is there is an unspoken elephant in the room every time one of us presents one of these surgical series. We present patients that have already had the gold standard of operation and operative pathology and try to extrapolate backwards to the patients that we are truly interested in, and the results of these tests we are trying to evaluate, such as radiology and EUS and biopsy and fluid characteristics, in part determine who actually gets an operation. Therefore, our evaluation of these tests is biased by the fact that we do not have surgical pathology on everyone who gets the tests. The population we are truly interested in is, however, patients who have cystic tumors in the general population. These two populations may be very different. On the one hand, surgical populations may be enriched for patients with malignant outcomes. On the other hand, as we have no knowledge of patients that never came to the operating room, we do not know what their outcomes were. And the only way, in my opinion, to answer these questions, which plague all of our surgical series, is to have prospective studies of cystic lesions and other lesions of the pancreas with broad-based inclusion criteria that predate considerably the decision for operation.

Thank you very much.

Cheong Lee, M.D. (Ann Arbor, MI): I agree with you wholeheartedly about the critical need for a prospective analysis to determine the best treatment for these lesions. To answer your first question in terms of our findings between side branch and main branch IPMN and why the relative risks of malignancy were almost equivocal, whereas the literature reports that main duct malignant lesions are more likely, this is likely due to the limited sample size in our study. However, we currently do not know the natural history of these lesions. We do not fully understand their biologic behavior due to the lack of a prospective series, as Dr. Tseng has mentioned. However, I do think that size does matter in these lesions, and regardless of tumor type, there is probably an overall lower incidence of malignancy when a lesion is smaller than 3 cm.

To answer your second question as to why there is a greater proportion of cancer in men, that is a very interesting point. We were surprised to find this in our study as well. I think indeed it could reflect a later diagnosis in men, but there could also be some unknown biological reason that these neoplasms behave differently in men. That calls for other studies to study that fact.

The third question you had was about the definition of what was called malignancy by cytopathologists. I agree, this is one of the limitations in our study in that there were variable criteria for the diagnosis of malignancy by cytopathologists between institutions. Some cytopathologists were conservative in their call for malignant atypia found in the cytologist's specimen. However, we noted the key words in the readings, such as high grade, atypical glandular cells, concern for adenocarcinoma, mucinous epithelium, and concern for malignancy. All these key words we noted as being positive for malignancy. Now, the cytology was considered benign when there was no mention of atypia and the lesions were considered low grade.

Lygia Stewart, M.D. (San Francisco, CA): How many of the patients that had mucin positivity and an elevated CEA greater than 192 had malignancy or did not have malignancy, and did you check for mucin? You did not mention it in your talk.

Dr. Lee: We did not specifically look for mucin, but in terms of the CEA level and cytology, we found there were a total of 15 patients who had a positive cytology and CEA levels for both the mucin-producing tumor and malignancy.

Mark P. Callery, M.D. (Boston, MA): What should you do with a 48-year-old woman with a 2.8-cm asymptomatic, except for anxiety, cyst in her uncinate process whose father passed away from pancreatic cancer at age 60?

Dr. Lee: Thank you. That is the key question.

Keith D. Lillemoe, M.D. (Indianapolis, IN): You gave 3.3% for your total percentage of asymptomatic tumors less than 3 cm. Can you give an actual percentage for those that you were able to prove that were mucin-producing tumors? The one cancer was in a mucin tumor. So what was your percentage for asymptomatic mucin-producing tumors?

Dr. Lee: There were three. All the premalignant types, there were three in the asymptomatic patients. So 6.6% of those patients had malignancy.

Dr. Lillemoe: No, no, you did not answer my question. How many asymptomatic less than 3-cm mucin-producing tumors did you have?

Dr. Lee: There was a higher percentage of mucin-producing tumors overall. Actually 79% of the tumors that we found that were less than 3 cm were mucin-producing tumors.

Dr. Lillemoe: Again, my question is, what is the incidence of cancer in asymptomatic mucinous-producing tumors than 3 cm in size?

Dr. Lee: It is 19%.

Dr. Lillemoe: Which is a lot higher than the mortality of a pancreaticoduodenectomy.

Dr. Lee: Correct.

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PGE_2 in Pancreatic Cyst Fluid Helps Differentiate IPMN from MCN and Predict IPMN Dysplasia

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Abstract Current management of intraductal papillary mucinous neoplasm (IPMN) according to recently published International Consensus Guidelines depends upon distinguishing it from mucinous cystic neoplasms (MCNs). We have previously shown that prostaglandin E_2 (PGE_2) is increased in pancreatic cancer tissue over normal controls. Thus, we hypothesized that PGE_2 level in pancreatic fluid differentiates IPMN and MCN and is a biomarker of IPMN dysplasia. Pancreatic fluid was collected in 65 patients at the time of endoscopy (EUS or ERCP) or operation (OR) and analyzed by PGE_2 enzyme-linked immunosorbent assay (ELISA). PGE_2 level was correlated with surgical pathologic diagnosis and dysplastic stage. Mean PGE_2 level (pg/μl) in IPMNs (2.2±0.6) was greater than in MCNs (0.2±0.1) ($p<0.05$). Mean PGE_2 level of IPMN by dysplastic stage was 0.1±0.01 (low grade), 1.2±0.6 (medium grade), 4.4±0.9 (high grade), and 5.0±2.3 (invasive). Among invasive IPMN, PGE_2 level dropped in advanced cases with pancreatic ductal obstruction by tumor (0.3±0) vs non-obstructed (8.6±2.9). PGE_2 level may help in distinguishing IPMN from MCN in patients with known mucinous lesions. PGE_2 level may also be an indicator of malignant progression of IPMN before ductal obstruction by tumor. Prospective evaluation will be necessary to evaluate the clinical role of PGE_2 level in pancreatic fluid.

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C. Max Schmidt and Michele T. Yip-Schneider contributed equally to this work.

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Keywords Prostaglandin E2 · PGE2 · Intraductal papillary mucinous neoplasm · Mucinous cystic neoplasm · Pancreatic cancer · Dysplasia · Biomarker · Pancreatic adenocarcinoma

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are papillary, mucin-producing, precancerous ductal lesions which can be unifocal or multifocal.[1–10] Current management of IPMN according to recently published International Consensus Guidelines depends upon distinguishing IPMNs from mucinous cystic neoplasms (MCNs).[1] MCNs have similar mucinous epithelial features as IPMN, and like IPMN, are precancerous. Histology of MCNs differs from IPMN, however, because they contain ovarian stroma. In addition, MCN are not multifocal or connected to the ductal system as are IPMN. IPMNs and MCNs are both gross lesions which are radiographically detectable and may often be differentiated by optimal imaging (magnetic resonance pancreatography, computed tomography) or endoscopy (endoscopic ultrasound or endoscopic retrograde pancreatography). Sometimes, pancreatic fluid analysis for amylase may suggest the presence or absence of a ductal connection. Despite optimal imaging, endoscopy, and pancreatic fluid amylase analysis, differentiation of IPMN from MCN may not be possible. Current treatment recommendations based upon the recently published International Consensus Guidelines dictate a different treatment algorithm for IPMN and MCN.[1] The treatment of asymptomatic side branch IPMNs may be nonsurgical or surgical contingent upon the existence of symptoms, mural nodules, or positive cytology. Conversely, the current recommendations for the treatment of MCNs are that they should all be resected in fit patients.[1] Distinguishing between IPMN and MCN is thus clinically relevant.

In addition to distinguishing MCN from IPMN, optimal treatment of IPMN should be based upon degree of IPMN dysplasia. There are no accurate preoperative markers of IPMN dysplasia. Cytology positive for malignancy is very specific for malignant IPMN, but positive cytology is not detected in many patients with malignant IPMN making it insensitive.[2] Thus, it is not a good indicator of nonmalignant IPMN. Novel biomarkers of IPMN dysplasia are needed to distinguish which IPMN lesions are nonmalignant and may be safely followed. We have previously shown that PGE_2 level, a marker of cyclooxygenase activity, is elevated in pancreatic cancer tumor tissue compared to adjacent normal tissue.[3] Furthermore, cyclooxygenase expression is greater with increasing PanIN and IPMN dysplasia.[3] Therefore, we hypothesized that prostaglandin E_2 (PGE_2) may aid in distinguishing IPMN and MCN and be a biomarker of IPMN dysplasia.

Materials and Methods

Assurances These studies have been conducted in strict compliance with the Indiana University School of Medicine Institutional Review Board

Patient samples Sixty-five patients signed informed consent for collection of pancreatic cyst and/or ductal fluid at the time of endoscopy (EUS or ERCP) or operation (OR). Surgical pathology was present in 58 patients. IPMN dysplasia was graded according to World Health Organization criteria, but updated terminology was used (adenoma = low grade dysplasia; borderline = medium grade dysplasia; carcinoma in situ = high grade dysplasia). Nonsteroidal anti-inflammatory (NSAID) medication use was recorded. Patients were excluded with more than occasional use of NSAID medications. Occasional use was defined as no more than two doses per week on average. Secretin was used in some cases where indicated to enhance ductal fluid yield. Specimens were placed immediately on ice after procurement and aliquoted for storage at −80°C. Samples were subsequently analyzed for PGE_2 to correlate with surgical pathologic diagnosis and dysplastic IPMN stage.

PGE_2 analysis Pancreatic fluid (50 μl) was analyzed by PGE_2 enzyme-linked immunosorbent assay (ELISA) (Amersham Biosciences, Piscataway, NJ). The assay is based upon competition between unlabeled PGE_2 and a fixed quantity of peroxidase-labeled PGE_2 for binding to a PGE_2-specific antibody bound to a plate. The amount of the bound PGE_2 peroxidase is measured by the addition of the substrate. Results are expressed as pg PGE_2 per microliter.

Statistics The Student's *t* test was used to compare two groups. Analysis of variance with Tukey's post test was used for multiple comparisons. Statistical significance was set at $p<0.05$.

Results

Pancreatic fluid from 65 patients was analyzed by PGE_2 ELISA. Surgical pathologic diagnosis in these patients was IPMN (29), pancreatic adenocarcinoma (12), MCN (11), serous cystadenoma (5), and pseudopapillary tumor (1). Among patients with IPMN, dysplastic grade was low grade dysplasia (2), medium grade dysplasia (12), high grade dysplasia (8), and invasive (7). Seven patients had pre- and post-secretin pancreatic ductal fluid sampling at ERCP. These patients did not have surgical pathology correlation. Three of these patients were thought to have sphincter of Oddi dysfunction, and the ERCP was non-diagnostic in the remaining four patients.

Exogenous Secretin Effect on PGE_2 Level in Pancreatic Ductal Fluid Secretin was used to enhance ductal fluid yield in 8% of pancreatic fluid samples analyzed. Thus, collections of pancreatic fluid before and after exogenous

secretin administration was performed in seven patients (each patient was used as their own control) to determine if there was a difference in PGE_2 after secretin administration (Fig. 1). Secretin, on average, decreased PGE_2 level fivefold (3±0.9 without secretin vs 0.6+0.2 with secretin; $p<0.05$). Subsequent PGE_2 analyses in this select minority of patients were adjusted to account for this difference.

Exogenous Non-Steroidal Anti-Inflammatory Drug Effect on PGE_2 Level in Pancreatic Ductal Fluid The mechanism of several NSAIDs is pharmacologic inhibition of the enzyme cyclooxygenase. Nonsteroidal anti-inflammatory medication use was recorded prospectively. No patients with more than occasional use of NSAIDs were analyzed as part of this study. Occasional use of NSAIDs was recorded in 12% of IPMN patients. For patients with occasional use, the PGE_2 level in the pancreatic fluid was compared to the mean PGE_2 level of the appropriate IPMN dysplastic category. The mean PGE_2 of patients with occasional use was not statistically different from the mean PGE_2 of the corresponding dysplastic category (Fig. 2).

PGE_2 Level in IPMN According to Pancreatic Fluid Collection Method Several methods of acquisition of pancreatic fluid were employed in patients with IPMN. Pancreatic fluid samples were taken via cyst aspiration during endoscopic ultrasound (EUS) or during surgery. Pancreatic fluid samples were also taken at the time of endoscopic retrograde pancreatography (ERCP) via ductal lavage or during pancreatic surgery via cannulation of the pancreatic duct. There was no difference in the PGE_2 levels in ductal fluid compared to cyst fluid when the same patient was used as their own control (Fig. 3). Similarly, there was no difference in PGE_2 levels in surgically acquired vs EUS-acquired cyst fluid fine needle aspiration (Fig. 4). Finally, there was no difference in PGE_2 levels in surgically acquired vs ERCP-acquired ductal fluid in a representative patient (12.5 vs 12.5 pg/μl).

PGE_2 Level in IPMN vs MCN PGE_2 level in pancreatic fluid was correlated with surgical pathologic diagnosis (Fig. 5). Mean PGE_2 level (pg/μl) in IPMNs (3.6+0.8) was greater than the mean PGE_2 level in MCNs (0.2+0.1) ($p<0.05$). The subgroup of noninvasive IPMNs (3.2±0.7) also had a greater mean PGE_2 level than MCNs ($p<0.05$). By comparison, serous cystadenomas (SCA) had a mean PGE_2 level of 0.2±0.1. One solid pseudopapillary tumor had a PGE_2 level of 0.04 pg/μl.

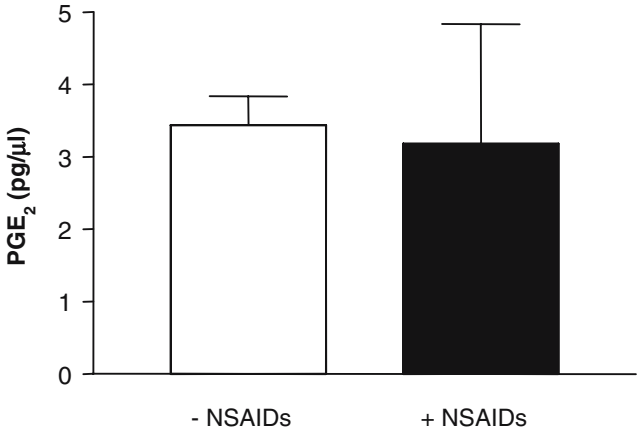

Figure 2 This figure depicts the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on pancreatic ductal fluid PGE_2 level. Six IPMN patients with occasional NSAID use underwent collection of pancreatic ductal fluid. Each patient was compared to the mean of their respective IPMN dysplastic category. There were no differences in PGE_2 (pg/μl) levels appreciated in IPMN patients with occasional NSAID use (3.2± 1.6) compared to mean of their respective dysplastic group categories (3.4±0.4), $p>0.05$ (t test).

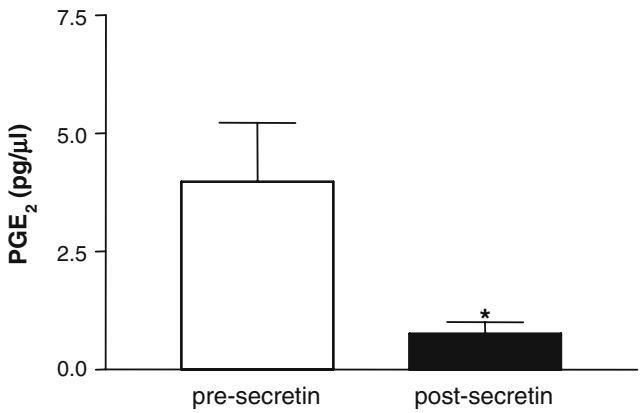

Figure 1 This figure depicts the effect of exogenous secretin administration on pancreatic ductal fluid PGE_2 level. Seven patients underwent collection of pancreatic ductal fluid via ERCP pre- and post-secretin administration. Each patient served as their own control. Post-secretin PGE_2 (pg/μl) levels (0.8±0.2) are decreased fivefold compared to pre-secretin PGE_2 levels (4.0±1.2), *p=0.03 (paired t test).

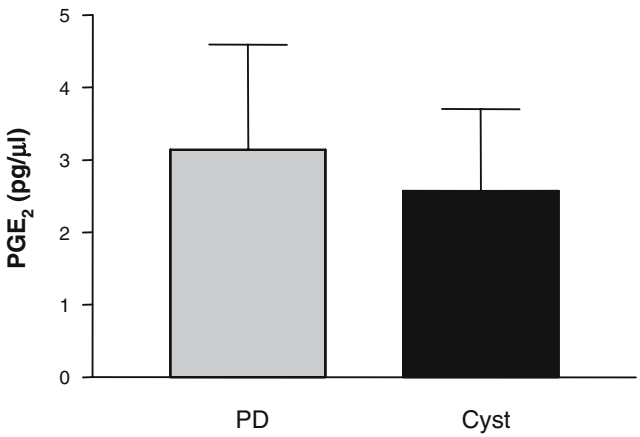

Figure 3 This figure compares the pancreatic ductal fluid PGE_2 level in cyst aspiration (Cyst) and pancreatic ductal lavage (PD) in IPMN patients who underwent both. Four IPMN patients underwent both fine needle aspiration and pancreatic ductal lavage of their IPMN. There were no differences in PGE_2 (pg/μl) levels in Cyst (2.6±1.1) compared to PD (3.1±1.5) pancreatic fluid, $p>0.05$ (paired t test).

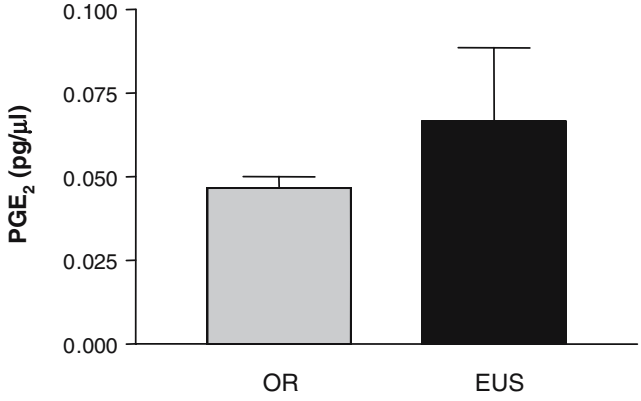

Figure 4 This figure compares the pancreatic ductal fluid PGE_2 level in intraoperative cyst aspiration (OR) to endoscopic ultrasound guided cyst aspiration (EUS) in IPMN patients who underwent both. Three IPMN patients underwent both fine needle aspiration at endoscopic ultrasound and intraoperatively of their IPMN. There were no differences in PGE_2 (pg/µl) levels in OR (0.05±0.0) compared to EUS (0.07±0.02) pancreatic fluid, $p>0.05$ (paired t test).

PGE_2 Level in IPMN According to Degree of Dysplasia

PGE_2 level was correlated with degree of IPMN dysplasia on final surgical pathology (Fig. 6). Mean PGE_2 level of IPMN by dysplastic stage was 0.1±0.01 (low grade), 1.2±0.6 (moderate grade), 4.4±0.9 (high grade), and 5.0±2.3 (invasive). Mean PGE_2 level showed a stepwise increase from low grade to invasive IPMN. By comparison, ductal fluid in patients with ductal adenocarcinoma not associated with IPMN had a mean PGE_2 level of 4.8±1.4 (Fig. 6).

Discussion

Intraductal papillary mucinous neoplasms remain poorly characterized and understood lesions.[1,4–10] The recently published International Consensus Guidelines are an attempt to establish some consistency in treatment of patients with IPMN.[1] Distinguishing IPMN from MCN is important in determining the management of patients with mucinous lesions of the pancreas. In this study, we examined the biomarker, PGE_2, in pancreatic fluid of patients with mucinous lesions of the pancreas to determine if this would help in the differentiation of IPMN from MCN. We also examined PGE_2 as a potential biomarker of IPMN dysplasia. Our study demonstrated that pancreatic fluid PGE_2 levels were significantly greater in IPMN than MCN and increased according to increasing IPMN dysplastic category.

Based upon our study findings, the use of pancreatic fluid PGE_2 may indeed help in the differentiation of IPMN from MCN. Nonetheless, the range of values of MCN does have significant overlap with the PGE_2 levels in IPMN low grade and part of the medium grade dysplasia categories. In light of this, it appears that only in cases of high PGE_2 levels can we say with confidence that a pancreatic mucinous neoplasm represents IPMN over MCN. One shortcoming of this study is that none of the patients with MCN had invasive cancer. Thus, the effect of invasive MCN (i.e., mucinous cystadenocarcinoma) on PGE_2 levels is unknown.

The use of pancreatic fluid PGE_2 indeed helps in determination of the degree of IPMN dysplasia in this

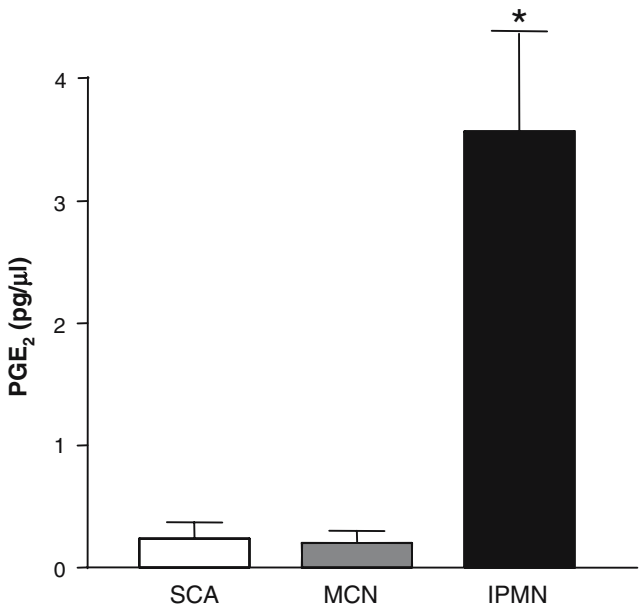

Figure 5 This figure compares the pancreatic fluid PGE_2 level according to surgical pathology. Mean PGE_2 level (pg/µl) in IPMNs (29) was 3.6±0.8 compared to MCNs (11) which was 0.2±0.1 $*p<0.05$, ANOVA, Tukey's post test. Five serous cystadenomas (SCA) had a mean PGE_2 level of 0.2±0.1.

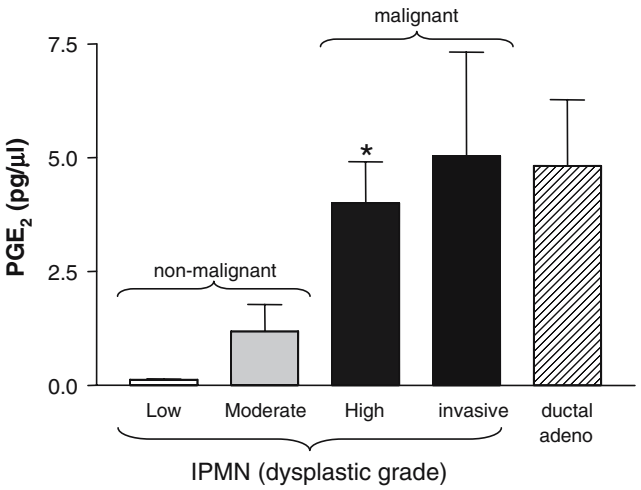

Figure 6 This figure compares the pancreatic fluid PGE_2 level according to IPMN dysplastic category. Mean PGE_2 level of IPMN by dysplastic stage was 0.1±0.01 (low grade, 2), 1.2±0.6 (moderate grade, 12), 4.4±0.9 (high grade, 8), and 5.0±2.3 (invasive, 7), $*p<0.05$ LGD vs HGD, and nonmalignant (LGD + MGD) vs malignant (HGD + invasive), t test. By comparison, ductal fluid in patients with ductal adenocarcinoma (12) not associated with IPMN had a mean PGE_2 level of 4.8±1.4.

retrospective study. In particular, in known IPMN, low PGE_2 levels were very predictive of nonmalignant IPMN based upon these data. Alternatively, high PGE_2 levels were not specific for malignant IPMN. This is because the range of values of malignant IPMN (high grade dysplasia and invasive) overlap with part of the medium grade dysplasia category. Examination of a histogram of PGE_2 in medium grade dysplastic IPMN patients reveals two distinct subgroups. One subgroup consisted of five patients who had a mean PGE_2 of 0.3 ± 0.1 which is more akin to the low grade dysplasia group. In contrast, the remaining seven patients had a mean PGE_2 of 5.1 ± 1.6, which is closer to the range of malignant IPMNs. If PGE_2 level alone were to dictate operative vs nonoperative treatment of IPMN, in light of these data, patients with higher PGE_2 in the medium grade dysplasia group would have unnecessary operation. One may speculate that these PGE_2 subgroups within the medium grade dysplasia category are clinically different, but with limited follow-up at this point, we are unable to adequately address this possibility. One shortcoming of this study is that the PGE_2 analysis is done at a single point in time. We would speculate that following serial pancreatic fluid PGE_2 levels longitudinally over time in a single patient with IPMN may provide further information helpful in the characterization of IPMN dysplasia.

Interestingly, we observed that pancreatic fluid levels of PGE_2 are low in advanced pancreatic cancer (IPMN associated or not) when complete pancreatic ductal obstruction occurs. Ductal obstruction may only be known in some patients after surgery. When known, however, complete ductal obstruction, particularly in the presence of a mass lesion and biliary obstruction, is invasive pancreatic cancer until proven otherwise. Determining the degree of dysplasia may not be clinically relevant in these patients, as the chance of invasive cancer is highly likely. It is unclear why the PGE_2 level is low under these circumstances, but we would speculate that it is because the pancreatic ductal fluid is no longer flowing across the IPMN cells. Alternatively, it could be that the cells producing PGE_2 are somehow switched off and/or the biology of the tumor no longer depends upon PGE_2.

We have previously examined cytology as a biomarker in IPMN. As previously published, we have shown that positive cytology is predictive of malignant IPMN.[2] Contrarily, negative cytology is not predictive of nonmalignant IPMN. Thus, pancreatic fluid PGE_2 level determination may complement cytology, as low PGE_2 levels are predictive of nonmalignant IPMN. Prospective evaluation will be necessary to determine the exact role of pancreatic fluid PGE_2 with or without cytology in clinical decision making. Longitudinal examination of pancreatic fluid PGE_2 level may also provide further information which would distinguish IPMN from MCN and indicate IPMN degree of dysplasia.

Finally, although it is unclear why PGE_2 level increases in pancreatic tissue and ductal fluid with increasing dysplasia, we would speculate that it is indicative of the important role inflammation may play in IPMN and may be a marker of chronicity of disease. We have been unable to establish a clear association with chronic pancreatitis or peripancreatic fibrosis in tissue and PGE_2 level in pancreatic fluid. In some cases, the opposite is seen where significant chronic pancreatitis such as in advanced IPMN with cancer and ductal obstruction demonstrates low PGE_2 levels in pancreatic fluid. Tissue studies (in patients with IPMN and/or pancreatic adenocarcinoma) previously published by the lab have shown that COX-2 expression in IPMN ductal cells is increased when the duct is surrounded by more than a cell layer thick of fibrous stroma.[3] This increased expression may occur before any mucinous or dysplastic change in the ductal cells. This data would suggest that periductal fibrosis may influence PGE_2 in the early stages of neoplasia.

In light of these data, further investigation into the role of pancreatic fluid PGE_2 level in characterizing IPMN dysplasia is warranted. Furthermore, pharmacologic inhibitors of cyclooxygenase deserve further study as chemopreventative agents in IPMN.

Conclusions

In this study, we examined the biomarker, PGE_2, in pancreatic fluid of patients with mucinous lesions of the pancreas to determine if this would help in the differentiation of IPMN from MCN. We also examined PGE_2 as a potential biomarker of IPMN dysplasia. Our study demonstrated that our pancreatic fluid collection methods were reproducible. Pancreatic fluid PGE_2 levels were shown to be greater in IPMN than MCN. Finally, pancreatic fluid PGE_2 levels were shown to be greater with increasing IPMN dysplasia. Prospective evaluation will be necessary to determine the exact role of pancreatic fluid PGE_2 level in clinical decision making in patients with IPMN. The authors do not, as a routine, send pancreatic ductal fluid samples for PGE_2 determination, but prospective evaluation is being performed in the context of an ongoing clinical trial.

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Discussion

Nipun B. Merchant, M.D. (Nashville, TN): Max, that was an excellent presentation, and I congratulate you on presenting this very compelling data that can potentially diagnose and distinguish IPMNs from other mucinous neoplasms. This assay clearly has the capability of having immediate clinical impact on the management of these patients. It is good to see from the previous talk and this one that we are beginning to understand these lesions better.

Based on your findings that PGE_2 levels were increased in pancreatic adenocarcinomas, I think it is logical to assess PGE_2 levels in cyst fluid. Based on this, I have several questions.

There is always a concern about using PGE_2 as a biomarker, as it is a significant biomarker of any inflammatory condition. So are you concerned that you may just be assessing an increase in inflammation, as these tumors progress from low grade dysplasia towards an invasive phenotype? Have you correlated the cyst levels of PGE_2 to actual tissue levels as you did with your pancreatic ductal adenocarcinomas? To extrapolate from your question on a previous talk, can you distinguish main duct lesions, that is, is there a difference in PGE_2 levels from main duct lesions and side branch lesions? I did not see in your talk if you were able to distinguish mucinous cystadenomas with mucinous cystadenocarcinomas based on differences in PGE_2 levels.

The other interesting thing I noticed is that your PGE_2 levels in the invasive IPMNs were significantly higher than PGE_2 levels seen in pancreatic adenocarcinoma. Can you speculate as to why that might be?

Lastly, I wanted to end on a comment. Last year at this meeting, we presented data showing that urinary PGE-M, which is a urinary metabolite of PGE_2, could be a potential biomarker in pancreas cancer, as it is significantly elevated in patients with cancer compared to normal controls. It seems as though this urinary biomarker might be ideal to evaluate in these patients to determine progression of disease or even following them for potential recurrence of disease.

Thank you for this excellent presentation.

C. Max Schmidt, M.D. (Indianapolis, IN): Thank you, Dr. Merchant, for your excellent questions. In response:

1. Inflammation: We believe that PGE_2 may be a biomarker of chronicity of disease. Inflammation/pancreatitis and other evidences of chronicity, e.g., exocrine/endocrine pancreatic insufficiency, may correlate with PGE_2 level and ultimately dysplastic state. PGE_2 level in pseudocysts/pancreatitis will undoubtedly have overlap with PGE_2 levels in dysplastic IPMN. Therefore, to clarify, this study is limited to known mucinous lesions. Thus, we envision application of PGE_2 as a biomarker in patients with a fairly certain diagnosis of a mucinous lesion, i.e., mucinous cyst CEA >200 ng/ml, cytology consistent with mucinous epithelium, or multifocal cysts consistent with multifocal side-branch IPMN. In other words, PGE_2 should not be used to distinguish chronic pancreatitis from mucinous cystic lesion of the pancreas.

2. PGE_2 tissue levels correlate? We have not measured PGE_2 level in pancreas tissue of progressive stages of IPMN dysplasia and correlated this with PGE_2 level in pancreatic cyst fluid. We have, however, looked at cyclooxygenase-2 expression, and this mirrors PGE_2 level in pancreatic cyst fluid.

3. Side branch vs main duct IPMN? Mucinous cystadenoma vs mucinous cystadenocarcinoma? This study was conceived as a side-branch IPMN study. Pancreatic cyst fluid samples on side branch invasive cancers, however, are uncommon. Thus, in this study, a significant number of invasive cancers are main type, whereas the other dysplastic IPMN are side branch type. Pancreatic cyst fluid on mucinous cystadenocarcinoma fluid was not available. These are limitations of the study which will only be remedied as we collect more of these precious samples to study through our own efforts or collaboration with others.

4. Why invasive IPMN has a higher PGE_2 level than ductal adenocarcinoma? Statistically, they are not different.

Mark P. Callery, M.D. (Boston, MA): What could be the cellular source of PGE_2 in these lesions?

Dr. Schmidt: Great question. Pancreatic cyst fluid when pelleted has a variety of cells including ductal epithelium, IPMN cells, inflammatory cells, hematopoietic cells, and supportive stromal cells. We are uncertain as to which is the predominant cellular source of PGE_2.

Dr. Callery: Have you tried to collect those and propagate them and study them?

Dr. Schmidt: We have tried collecting them and propagating them. We have been able to achieve attachment of IPMN cells but have been unable to successfully passage them to date.

L. William Traverso, M.D. (Seattle, WA): Dr. Schmidt, your results are very provocative and made me think a little bit more about the problem we have in the practical sense of mucinous cystic neoplasms vs IPMNs. I would follow Dr. Callery's question and ask you what cell produces PGE_2? Is it possible that PGE_2 is not present inside an obstructed duct or cyst? A MCN may not have PGE_2 because there is no duct for it to communicate with and that the cell of origin may be atrophied in the ductal obstruction. The pathologist will not make a diagnosis of mucinous cystic neoplasm in the head of the pancreas in a man because there is no ovarian stroma. You will never see one made in a man. So any cystic neoplasm in the head with or without a ductal connection will not help the pathologist diagnose MCN. If there is no ovarian stroma, it will not be called a mucinous cystic neoplasm. Therefore, the pathologist could really use a biomarker in their classification system as they are trying to do with the new version of the AJCC staging system.

So my question would be if PGE_2 could be seen in the wall in an immunohistochemical study in an IPMN and it was also *not* seen in the wall of a MCN, it would further help them make a diagnosis. We will never see a mucinous cystic neoplasm in the head of the pancreas with the current classification. So this is really an assistance to the pathologists. The next time they meet in Park City like they did in the mid 1990s to devise the WHO classification, they could use this biomarker as an assistance to help in practical application of it in the future. Do you think you can find PGE_2 in the cell?

Dr. Schmidt: Thank you Dr. Traverso. PGE_2 immunohistochemistry is being performed by our lab presently, but we have not established optimal conditions to date. We are hopeful that we will determine the cell(s) or origin.

COX-2 (upstream from PGE_2) has been characterized via immunohistochemistry in the ductal epithelium of IPMNs and PanINs by our group and others and demonstrates a similar positive correlation with progressive IPMN and PanIN dysplasia.

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Suboptimal Weight Loss after Gastric Bypass Surgery: Correlation of Demographics, Comorbidities, and Insurance Status with Outcomes

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Abstract Although Roux-en-Y gastric bypass surgery (RYGBP) is safe and effective at achieving weight loss in the majority of severely obese patients, a subset fails to achieve expected weight loss outcomes. Factors associated with poor weight loss are not well defined. Patients undergoing open RYGBP using a standardized surgical technique and clinical pathway by a single surgeon at a dedicated bariatric center were reviewed. Suboptimal weight loss was defined as failure to lose at least 40% excess body weight by 12 months postoperatively. Of 555 consecutive patients who underwent RYGBP from 1999 to 2004, a 12-month follow-up was available for the 495 (89%). Suboptimal weight loss occurred in 55 (11%) and was associated on unadjusted bivariate analysis with increased body mass index (BMI; $p=0.0002$), diabetes mellitus ($p=0.0002$), Medicaid insurance ($p=0.04$), and male sex ($p=0.01$). On adjusted multivariate analysis, increased BMI ($p=0.003$), diabetes ($p=0.002$), and male gender ($p=0.04$) were associated with suboptimal weight loss, but type of insurance ($p=0.11$) was not. Medicaid patients were younger ($p=0.01$) and had higher BMI ($p=0.0002$). Suboptimal weight loss after RYGBP appears to be associated with greater BMI, male sex, and diabetes but not type of insurance. This study may help identify patients who could benefit from increased perioperative education and counseling or selection of procedures with greater malabsorption.

Keywords Bariatric surgery · Gastric bypass · Morbid obesity · Suboptimal weight loss

Introduction

Morbid obesity represents an increasingly significant public health issue in the USA. The prevalence of obesity, defined as a body mass index (BMI) of ≥30 kg/m^2, has increased over the past 30 years at alarming rates. Between 1986 and 2000, the rate of obesity (BMI≥30 kg/m^2) has doubled, morbid obesity (BMI≥40 kg/m2) has quadrupled, and super obesity (BMI≥50 kg/m^2) has quintupled in adults in the USA.[1] This rise in obesity prevalence is more pronounced in women, with an estimated 2.9% of men and 4.8% of women in 1999–2000 being morbidly obese compared to 2.8% of men and 6.9% of women in 2003–2004.[2] Although there remains a multitude of undefined contributing factors, some important reasons for these trends include an increasing prevalence of obesity in children and adolescents, increasingly sedentary lifestyles, and easier access to caloric-dense foods. In the long term, morbid obesity may contribute to a large number of medical and psychosocial problems as well as an increase in premature mortality.

Of the currently available management options for morbidly obese individuals, bariatric surgery has been demonstrated to be the most effective treatment for achieving significant and sustained weight loss.[3,4] In the USA, Roux-en-Y gastric bypass surgery (RYGBP) is the gold standard of bariatric operations[5] and is the most commonly

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performed procedure to treat morbid obesity, accounting for 80% of all bariatric procedures performed in 2002.[6] RYGBP has been demonstrated to be safe and effective at achieving weight loss in the majority of severely obese patients[4,7] and has been associated with a decreased risk for development of cardiovascular, neoplastic, endocrine, infectious, psychiatric, and neurologic disorders.[8]

Unfortunately, there remains a subset of patients who undergo bariatric surgery and fail to achieve expected weight loss outcomes. Factors associated with poor or suboptimal weight loss (SWL) have not been well defined. In addition, it is unclear if SWL impacts on postoperative resolution of comorbidities, such as hypertension and diabetes. In this study, we sought to delineate factors associated with poor weight loss outcomes and postoperative comorbidity resolution after RYGBP.

Material and Methods

All patients undergoing open RYGBP by a single surgeon (THM) at the Johns Hopkins Bayview Medical Center between 1999 and 2004 were registered in an Institutional Review Board-approved database. Patient selection, including evaluation and approval by a multidisciplinary team, was performed according to the National Institutes of Health consensus guidelines for treatment of the morbidly obese patient.[5] Patients were counseled before and after surgery by bariatric dieticians and a dedicated psychiatrist and were encouraged to participate in monthly support group meetings.

Data obtained for this study included each patients's age, sex, race, height, weight, presence of comorbid conditions, and type of insurance. The diagnoses of hypertension, coronary artery disease, sleep apnea, diabetes mellitus, and dyslipidemia were assigned based on self-reported history of the condition or use of specific medications for each condition. Ideal body weight, as determined by Metropolitan Life Insurance tables, was used to calculate excess body weight (EBW). Percent excess weight loss (EWL) was calculated as actual weight lost divided by EBW.

The RYGB procedure was standardized to include a 20-ml proximal gastric pouch, 40-cm biliopancreatic limb, and 150-cm Roux-en-Y limb. The Roux-en-Y gastrojejunostomy was created using a retrocolic retrogastric approach, and the gastrojejunostomy anastomosis was performed with a double-layer, handsewn technique. The jejunojeunostomy anastomosis was similarly performed in a double-layer, handsewn, side-to-side fashion.

After surgery, a standardized clinical pathway was implemented. Patients remained without oral intake postoperatively for approximately 48 h and then underwent fluoroscopic swallow study to assess the gastrojejunostomy. Patients were subsequently advanced with their diet and discharged on postoperative day 3 or 4 under optimal clinical conditions.

After discharge from the hospital, patients were assessed at routine 3-month intervals for weight loss for the first year after surgery and at 6-month intervals thereafter. SWL was defined as a failure to lose at least 40% of EBW by 1 year postoperatively. Patients in whom follow-up was not available at 1 year after RYGBP were excluded from the study. Patients requiring medications for the treatment of diabetes or hypertension were assessed at 1 year after surgery for resolution of these conditions. Diabetes or hypertension was defined as resolved when medications had been fully discontinued and were no longer required.

Statistics were obtained using established methods. Statistical significance was accepted for $p<0.05$. Unadjusted bivariate comparisons of continuous variables were performed using the Mann–Whitney rank sum test, and comparisons of categorical variables were performed using a χ^2 test. Multiple logistic regression was used to develop an adjusted multivariate model with odds ratio tests. Data are expressed as means where appropriate. Data analyses were performed using Stata 7.0 (College Station, TX, USA).

Results

From January 1, 1999 to December 31, 2004, 555 consecutive patients underwent open RYGBP for surgical treatment of morbid obesity. Follow-up at 1 year was available in 495 patients (89%); these patients compose the cohort for this study. Mortality occurred in two patients (0.36%), and there was no staple line or anastomotic leaks in this series. Demographic data and preoperative comorbidities are depicted in Table 1. The mean age of patients was 42 years, 85% was white, and 18% was male. Mean preoperative weight was 155 (range 92–288) kg; mean BMI was 55 (range 37–96) kg/m^2; and mean EBW was 92 (range 36–215) kg. Obesity-related comorbidities of diabetes (30%), dyslipidemia (24%), hypertension (50%), and sleep apnea (36%) were relatively common. A small subset of patients had Medicare (5%) or Medicaid (7%) insurance.

At 12-month follow-up, mean EWL was 60±16% for the entire cohort. SWL occurred in 55 patients (11%). On unadjusted bivariate analysis, SWL was associated with higher preoperative BMI ($p=0.0002$), presence of diabetes mellitus ($p=0.0002$), Medicaid insurance status ($p=0.04$), and male sex ($p=0.01$; Table 2). Age, race, Medicare insurance status, and other preoperative comorbidities (coronary artery disease, hypertension, dyslipidemia, and sleep apnea) did not predict SWL. Although diabetes mellitus was associated with SWL, the rate of SWL with different types of treatment (insulin dependent, oral

Table 1 Demographic and Preoperative Clinical Data in Patients Undergoing RYGBP

	N (%)
Total	495 (100%)
Mean age (range, years)	42 (19–66)
Male sex	91 (18%)
Race	
White	419 (85%)
Black	73 (15%)
Other	3 (1%)
Type of insurance	
Commercial/HMO	438 (88%)
Medicare	27 (5%)
Medicaid	30 (7%)
Mean BMI (range, kg/m^2)	55 (37–96)
Mean preoperative weight (range, kg)	155 (92–288)
Mean EBW (range, kg)	92 (36–215)
Comorbidities	
Diabetes	147 (30%)
Dyslipidemia	120 (24%)
Hypertension	247 (50%)
Sleep apnea	178 (36%)
Coronary artery disease	29 (6%)

BMI Body mass index, *EBW* excess body weight

hypoglycemic medications, or diet controlled) was not significantly different.

On multivariate analysis, higher BMI (p=0.003), diabetes mellitus (p=0.002), and male sex (p=0.04) remained significantly associated with SWL, but Medicaid insurance status did not (p=0.11; Table 3). When comparing patients with Medicaid insurance to other forms of insurance, Medicaid patients tended to be younger (p=0.01) and have higher BMI (p=0.0002; Table 4).

Although, in the current study, SWL was defined as failure to achieve at least 40% EWL as the primary outcome measure, others have reported a less stringent cutoff of less than 50% EWL. Overall, 135 patients (27%) failed to achieve at least 50% EWL at 1 year. Similar to the results observed with a cutoff of 40%, preoperative BMI and diabetes as well as Medicaid insurance were significantly associated with less than 50% EWL on multivariate analysis.

With respect to comorbidities and their resolution as a marker of success, follow-up was available in 125 of 130 patients (96%) with preoperative diabetes requiring medications. Of the patients with SWL, 17 of 25 patients (68%) had complete resolution of diabetes; among the 100 patients with successful weight loss, the result was similar (80%; p=0.31). Patients with preoperative hypertension had follow up available in 237 of 247 patients (96%). In contrast to diabetes, resolution of hypertension did appear to be impacted by SWL. In the SWL group, 16 of 30 patients

Table 2 Bivariate Unadjusted Analysis Correlating Preoperative Clinical Factors and Suboptimal Weight Loss in Patients Following RYGBP

	Suboptimal weight loss (*N*=55)	Successful weight loss (*N*=440)	*p* value
Mean age, years	43 (25–66)	42 (19–62)	NS
Male sex	17 (30%)	74 (17%)	0.01
White	42 (76%)	377 (86%)	NS
Medicare insurance	3 (5%)	24 (5%)	NS
Medicaid insurance	7 (16%)	23 (6%)	0.04
Mean BMI, kg/m^2	60 (40–96)	54 (37–95)	0.0002
Diabetes	29 (53%)	118 (27%)	0.0002
Dyslipidemia	15 (27%)	105 (24%)	NS
Hypertension	34 (62%)	213 (49%)	NS
Sleep apnea	23 (41%)	155 (36%)	NS
Coronary artery disease	6 (11%)	23 (5%)	NS

Data expressed as *N* (%) for nominal variables or mean (range) for continuous variables.
BMI Body mass index, *NS* not significant

Table 3 Multivariate Adjusted Analysis Correlating Preoperative Clinical Factors and Suboptimal Weight Loss in Patients Following RYGBP

	Odds ratio	95% confidence interval	*p* value
Male sex	1.9	(1.3, 3.5)	0.04
Medicaid insurance	2.0	(0.7, 3.2)	NS
BMI	8.5	(2.0, 36.7)	0.003
Diabetes	2.6	(1.5, 4.8)	0.002

BMI Body mass index, *NS* not significant

Table 4 Correlation of Medicaid Insurance Status and Preoperative Clinical Factors

	Medicaid insurance	Other (non-Medicaid) insurance	*p* value
Overall	30 (7%)	465 (94%)	–
Mean age, years	38 (22–54)	43 (19–66)	0.01
Male sex	4 (13%)	87 (19%)	NS
White	22 (73%)	397 (85%)	NS
Mean BMI, kg/m^2	62 (38–96)	54 (37–91)	<0.0001
Diabetes	11 (37%)	136 (29%)	NS
Dyslipidemia	6 (20%)	114 (25%)	NS
Hypertension	12 (40%)	235 (51%)	NS
Sleep apnea	12 (40%)	166 (36%)	NS
Coronary artery disease	2 (7%)	27 (6%)	NS

Data expressed as *N* (%) for nominal variables or mean (range) for continuous variables.
BMI Body mass index, *NS* not significant

(53%) were found to have complete resolution of hypertension. Patients with successful weight loss, in contrast, had complete resolution of hypertension significantly more often, in 163 of 207 patients (79%, $p=0.005$).

Weight loss information at 2 years follow-up was available in 366 patients (74%). In the subgroup with SWL, 34 of the 55 patients (62%) had follow-up at 2 years with an average EWL of 41±12%, compared to 34% at 1 year. Patients in the successful weight loss group had a 2-year follow-up in 332 patients (75%) and an average EWL 69±16%, compared to 63% EWL at 1 year. Overall, the EWL at 2 years for the entire cohort was 67±18%.

Discussion

The current study examines a large retrospective cohort of patients who underwent open RYGBP performed by a single surgeon using a standardized technique. We found an average EWL of 60% at 1 year and 67% at 2 years after surgery. This degree of weight loss is consistent with previous studies including a recent meta-analysis by Buchwald et al.,[9] which included over 7,000 patients in 44 studies and reported a mean EWL of 62% at 1 year after gastric bypass. We observed SWL (less than 40% EWL at 1 year) in 55 of 495 patients (11%) after gastric bypass. Preoperative factors associated with poor weight loss outcomes on multivariate analysis included increased BMI, presence of diabetes, and male sex. Other factors such as age, race, and type of insurance did not appear to correlate with percent EWL.

Although factors associated with SWL after gastric bypass have not been well defined, the most consistent factor previously associated with less favorable weight loss outcomes is greater preoperative BMI. Our study, along with several others,[10–13] demonstrates inferior weight loss in patients who are super-obese (BMI≥50 kg/m^2) or have a higher BMI. The underlying etiology of why heavier patients do worse with respect to percent EWL as an outcome is unclear. This may in part be because of a reduced level of activity in these heavier patients with decreased caloric expenditures postoperatively. There may also be genetic or intrinsic metabolic differences in patients who are "super-obese" that result in relative inferior weight loss after surgery compared to less heavy patients. Lutfi et al.[14] reported a series of 180 patients undergoing laparoscopic gastric bypass and also identified higher preoperative BMI, as well as being married, as significant predictors of poor weight loss. In a similar study, Ma et al.[15] found that higher preoperative BMI, older age, female sex, and diabetes correlated with inferior weight loss outcomes. In the current study and others, diabetes also appears to be associated with SWL.[15–17] Our results suggest, however, that the type of diabetic treatment may not be a significant predictor of poor weight loss.

Few studies have addressed weight loss outcomes after bariatric surgery with respect to socioeconomic or medical insurance status. In this series, patients using Medicaid were significantly more likely to have SWL on unadjusted bivariate analysis. This association was not statistically significant on multivariate analysis, however, probably because Medicaid patients were more likely to have a higher preoperative BMI ($p<0.0001$) compared to patients with other insurance. Furthermore, Medicaid patients in the current study were significantly younger compared to the rest of the cohort ($p=0.01$). In an earlier series examining 131 consecutive patients who underwent vertical gastric banding, Durkin et al.[18] found no difference in weight loss according to insurance status. In addition, although several studies have demonstrated increased mortality rates and complications after bariatric surgery in Medicare patients,[19,20] we did not observe any difference in weight loss outcomes in patients with Medicare insurance compared to the rest of the cohort.

Percent EWL is the most common outcome measure used as a surrogate for overall success for bariatric surgical procedures. In the current study, we defined SWL as less than 40% EWL, roughly similar to other studies that have used less than 50% EWL[17,21,22] or greater than one standard deviation from the mean[14] as indicators of weight loss failure. The cutoff of 40% EWL was chosen to maximize potential differences between the two study groups and to isolate factors with those patients who clearly did not attain successful weight loss.

Perhaps as important and, possibly, more important as an index of success, however, is resolution of obesity-related comorbid disease, such as hypertension and diabetes. Overall resolution of diabetes in the current study was 78%, consistent with an 83.7% resolution rate reported in a recent meta-analysis.[9] We found that resolution of diabetes did not correlate with the degree of weight loss and did not differ between the SWL group and those achieving greater weight loss. Given that hypoglycemic medications can often be discontinued early in the postoperative period, before significant weight loss, it is possible that mechanisms other than absolute weight loss, such as bypass of the duodenum and alteration of the "entero-insular" axis, may account for changes in glucose homeostasis.[23,24] In contrast to diabetes, however, resolution of hypertension did appear to be impacted by SWL in the current study. Hypertension was completely resolved in 76% of patients overall, with the successful weight loss group demonstrating a greater proportion of patients with resolution compared to the SWL group (79 versus 53%, $p=0.005$).

The preoperative identification of patients at risk for SWL after gastric bypass is important for several reasons.

Risk factors such as those identified in the current study can help target patients who may benefit from increased perioperative counseling and dietary supervision. Although controversial, counseling patients to lose weight in the preoperative period has been associated in some series with improved postoperative weight loss outcomes.[25] It remains unclear, however, if patients specifically at risk for poor weight loss can improve their outcomes through increased dietary supervision alone. Furthermore, a better understanding of weight loss and comorbidity outcomes can help patients to have more realistic individual expectations after RYGBP. Modification of the operative procedure may also be indicated based on preoperative risk factors. Some studies suggest that bariatric procedures with a greater degree of malabsorption, such as the duodenal switch[21] or a more distal RYGBP,[11,22,26] may yield better outcomes in patients who have higher BMI, compared to a traditional RYGBP. In addition, analogous to reports where vertical banded gastroplasty has been converted to RYGBP in the setting of poor weight loss outcomes,[27] several groups have reported that converting from a standard RYGBP to a malabsorptive distal bypass can augment weight loss in patients who demonstrate insufficient weight loss with the primary procedure.[28,29]

There are several limitations to the current study. First, although the cohort is large and treated using a uniform surgical technique and clinical pathway, the series represents only a single institutional, retrospective experience. Conclusions from this study are based upon follow-up at 1 and 2 years after surgery and fail to account for possible ongoing weight loss after this time period or for possible late weight regain. Outcome measures at 5 and 10 years post-surgery may provide more valid indices of success. It is our experience, however, that although higher BMI patients may take longer to reach their weight loss nadir, nearly all weight loss occurs in the first 2 years after gastric bypass. Furthermore, although follow-up was good at 1 year (89%) and 2 years (74%), the results of this study would be further strengthened by more complete follow-up both short and long term.

Conclusion

RYGBP remains an effective and safe procedure for achieving weight loss in the great majority of severely obese patients. SWL appears to be associated with greater BMI, male sex, and diabetes. When these factors are accounted for, type of insurance does not appear to be predictive of poor weight loss. These factors may help to identify patients who might benefit from increased perioperative education and counseling and, perhaps, alterations in surgical treatment planning.

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Discussion

Michael G. Sarr, M.D. (Rochester, MN): This is a vexing problem for the bariatric surgeon. Do you really think that if you can identify these patients that you have an effective intervention preoperatively to offer?

Genevieve B. Melton, M.D. (Baltimore, MD): Dr. Sarr, thank you for your question. Yes, I think that there is some evidence that there are things that we can do to help these patients. First, with respect to preoperative interventions, the Stanford group, has reported that you can have improved weight loss outcomes if patients are encouraged to lose weight preoperatively. Second, with the super obese patients with BMIs over 50, there is evidence that doing a more distal gastric bypass, a Roux limb usually between 100 to 250 cm, can help patients lose more weight. Also, with the duodenal switch, similar improved weight loss outcomes have been noted in the subset of the heaviest patients.

John M. Kellum, Jr., M.D. (Richmond, VA): I too enjoyed your paper. I want to focus on the diabetic problem, because we recently looked at our database of over 4,500 patients and found that indeed they do lose less excess weight. Even though statistically it is very significant, at $P<0.0001$, we are talking only about a 67% versus a 60% loss of initial excess weight. And I agree with your findings that it doesn't affect resolution of diabetes. It is known that patients with Type 2 diabetes all have insulin resistance, which slows down metabolic rate. So I am wondering if any type of preoperative counseling will affect weight loss in the diabetic? I hope this won't be used as a reason not to do gastric bypass in the diabetic patient.

Dr. Melton: Dr. Kellum, thank you for your question and comments. I think in fact that this study suggests that we get very good resolution of diabetes after Roux en Y gastric bypass. Evidence from the Rubino group with an animal model has demonstrated that if you bypass the duodenum and proximal jejunum that you often will have resolution of diabetes. In fact, this has been done with patients in India, Mexico and Brazil where they have bypassed the duodenum and have observed resolution of diabetes.

Perhaps the best study out there with respect to diabetes resolution with gastric bypass surgery is from the University of Pittsburgh from Dr. Schauer's group, which also has shown very good resolution, about 80%, of diabetes, but they have five year data. They demonstrated that those with a shorter duration of diabetes were more likely to have resolution, as well as diet controlled diabetics. In addition, those that lose more weight following surgery tend to resolve more often, as well.

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Endoscopic Ultrasound with Conventional Probe and Miniprobe in Preoperative Staging of Esophageal Cancer

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Abstract
Background Using an endoscopic ultrasound (EUS) miniprobe, even highly stenotic esophageal cancers precluding the passage of a conventional probe can be examined without prior dilatation.
Objective To assess: (1) staging accuracy of conventional EUS probe and miniprobe, (2) variables influencing staging accuracy, (3) endoscopic features predicting tumor stage.
Methods Ninety-seven consecutive patients with esophageal cancer undergoing complete surgical resection were included. Preoperative EUS was performed using a conventional probe in nonstenotic tumors and a miniprobe in stenotic tumors. Accuracy of EUS for T and N stages was compared to pathohistological staging.
Results Overall EUS staging accuracy was 73.2% for T stage and 74.2% for N stage. It was similar for the miniprobe used in stenotic tumors vs the conventional probe used in nonstenotic tumors. Based on EUS, 84.5% of the patients would have been assigned to the appropriate therapy protocol (primary surgery vs neoadjuvant therapy). Endoscopic tumor features had no influence on staging accuracy. Tumor length >5 cm predicted advanced T and nodal positive stages.
Conclusions The miniprobe allows adequate EUS staging of stenotic esophageal tumors precluding the passage of a conventional probe. Therefore, dilatation therapy of stenotic cancers to conduct conventional EUS should be avoided.

Keywords Esophageal cancer · Staging · Endoscopic ultrasonography · Stenosis

Introduction

The prognosis of esophageal cancer in terms of long-term survival is poor with an overall 10–20% survival rate at 5 years after diagnosis.[1] Whereas patients with localized early disease clearly benefit from complete surgical resection, there is increasing evidence that neoadjuvant chemoradiation is superior to surgery alone for patients with locally advanced tumors.[2–4] Accurate local cancer staging is of utmost importance, as the initial cancer stage triggers the different treatment strategies.

Endoscopic ultrasound (EUS) plays an important role in routine staging of esophageal cancer. Being introduced into clinical practice in the nineties, the accuracy of EUS has repeatedly been reported to be 70–90% for T stage[5–8] and 65–80% for N stage.[7–10] The exact preoperative staging seems to translate into a better selection of patients for neoadjuvant treatment protocols as shown in a retrospective study in which patients with EUS had a survival benefit compared to those with CT scan alone.[11]

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However, tumor stenosis prohibiting the passage of a conventional large diameter EUS probe is a common clinical problem at the time of patient presentation. Non-traversability rates of up to 45% have been reported.[7] Therefore, dilatation of tumor stenosis before EUS has been recommended to allow a diagnostic EUS with a standard EUS probe, but this procedure leads to a significant risk of tumor perforation of up to 24%.[12]

The use of an EUS miniprobe being introduced via the working channel of a flexible endoscope allows the complete EUS examination of even high-grade stenotic tumors. However, the validity of miniprobes for staging of stenotic esophageal cancer is a topic of recent discussion.[7] Some authors argue that the limited depth of penetration of miniprobes restricts their use for staging as the full extent of the cancer and of adjacent lymph node groups may be beyond view.[10,13]

In this study, the following algorithm for preoperative endosonographic staging of esophageal cancer was evaluated. In nonstenotic tumors, a conventional EUS probe was used. In stenotic tumors, which prohibit the passage of the conventional probe, an EUS miniprobe was used. Dilatation therapy to allow an examination with the conventional probe was never performed. The staging accuracy of this concept was evaluated in identifying patients eligible for neoadjuvant treatment protocols. We wanted to clarify if the use of a miniprobe in stenotic tumors makes the hazardous dilatation therapy unnecessary. We also questioned whether tumor characteristics influence staging accuracy and whether endoscopic features allow a prediction of tumor stage.

Patients and Methods

Between January 2001 and July 2004, 97 consecutive patients fulfilled the following inclusion criteria: histologically diagnosed esophageal cancer or cancer of the gastroesophageal junction (squamous cell cancer and adenocarcinoma), preoperative EUS, and complete tumor resection with two-field lymphadenectomy. As the postoperative pathohistological findings served as "gold standard" for the TNM staging, all patients without complete tumor resection were excluded. As potential tumor regression during neoadjuvant treatment makes pathohistological determination of the initial tumor stage impossible, patients receiving preoperative neoadjuvant treatment were also excluded. Written consent was obtained from all patients before endoscopy and EUS, and the study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975. All EUS examinations were performed by one endoscopist (D.T.). The examiner was not blinded to other available clinical information (CT scan, endoscopy, etc.). All patients had a diagnostic endoscopy immediately before EUS. Grade of tumor stenosis and tumor length were routinely assessed. In case of high-grade stenosis, which prohibits the passage of the endoscope, complete endoscopy was omitted and tumor length was estimated by EUS.

EUS was performed with a conventional probe (optical Pentax FG 38-UX echo endoscope, diameter 13.5 mm, 7.5 MHz), if the passage of this probe was possible without dilatation therapy. If tumor stenosis prohibited the passage of the conventional probe, EUS was performed with an EUS miniprobe (Fujinon PL 222 6–15, diameter 2.6 mm, 15 MHz) introduced via the working channel of a flexible endoscope. Depth of tumor penetration into the five layers being identified by EUS indicated the T stage. Lymph nodes were considered positive, if they met at least one of the following criteria: larger than 10 mm, clearly delineated borders, hypoechoic or internal echo characteristics similar to the primary tumor, roundly shape.

EUS staging was compared to the postoperative pathohistological staging, allowing the calculation of accuracy, overstaging, and understaging for T and N stages. Pathohistological N1 and N2 stages were combined as "N positive" stage.

Endoscopic features (stenotic vs nonstenotic, traversability vs nontraversability, tumor length <5 cm vs >5 cm) were used as diagnostic tests for discriminating T0–2 vs T3 stages and N negative vs N positive stages. For each test, accuracy, sensitivity, specificity, and positive and negative predictive values were calculated.

Fisher's exact test was used for the comparison of subgroups, considering $P<0.05$ significant.

Results

The mean age of the patients was 64.7 years (SD=10.7, range 30–83). The majority of tumors were adenocarcinomas (71%). Of the tumors, 81% were localized in the esophagus, whereas 19% were localized in the gastroesophageal junction (Siewert classification: type II). Almost 60% of tumors were not traversable by the conventional EUS probe because of tumor stenosis. Using the EUS miniprobe, all patients could be completely assessed by EUS without any complications. Pathohistological staging revealed most tumors being locally advanced (Table 1).

Overall staging results for T and N stages using the miniprobe or the conventional probe are given in Tables 1 and 2. It is surprising to note that two patients with uT1 carcinoma were diagnosed as noninvasive carcinoma in situ by histopathology. Overall staging accuracy was 73.2% for T stage and 74.2% for N stage. The accuracy for discriminating early T stages (T0–2) vs locally advanced stages (T3) was 82.5%. Using the EUS staging results for

Table 1 Overall Staging Results for T Stage (n=97), EUS Staging (uT) vs Pathohistological Staging (pT)

	pT0	pT1	pT2	pT3
uT1	2	13	1	
uT2		6	16	12
uT3			5	42

Accuracy=73.2% (63.2–81.7), overstaging=13.4% (7.3–21.8), understaging=13.4% (7.3–21.8). Two cases of noninvasive carcinoma in situ were misinterpreted as invasive uT1 carcinoma.
95% confidence interval given in parentheses.

determining the therapy regimen (primary surgery if T1–2 and N negative, neoadjuvant therapy if T3–4 and/or N positive), 84.5% of the patients would have been assigned to the correct therapy. Of the patients, 8.2% would not have received neoadjuvant therapy although indicated (undertreatment), whereas 7.2% would have been overtreated with neoadjuvant therapy.

Table 3 shows the influence of the EUS probe used, of tumor-related factors, and of endoscopic features on the staging accuracy. The conventional probe (used in nonstenotic cancers) and the miniprobe (used in stenotic cancers) showed comparable accuracies for T and N stages. There was no significant difference in the distribution of T and N stages between the two groups (data not shown). There was a nonsignificant trend toward increased T staging accuracy in T3 tumors compared to T1–2 tumors. Endoscopic traversability, tumor histology, and tumor length had no influence on T and N staging accuracies. A learning curve was observed, as the second set of patients (nos. 50–97) had a significantly better T staging accuracy than the first set of patients (nos. 1–49; 83.3% vs 63.3%, P=0.038).

Mean tumor length was 4.7 cm (SD=2.75 cm, range 1–12 cm). Mean tumor length was shorter for T0–2 tumors compared to T3 tumors (3.8 vs 6.2 cm). Table 4 shows the accuracies for differentiation of T0–2 vs T3 and N negative vs N positive, if traversability for the conventional probe, endoscopic traversability, and tumor length (with a length of >5 cm indicating T3) were used as diagnostic tests. Tumor length showed an accuracy for T1–2 vs T3 differentiation that was not significantly inferior to the respective values obtained by EUS (accuracy=71.3%, sensitivity=60.4%, specificity=84.6%). The same was found for N staging (accuracy=62.1%, sensitivity=51.9%, specificity=77.1%). In contrast, neither traversability for conventional EUS probe nor endoscopic traversability were useful for differentiation of T and N stages.

Discussion

Accurate preoperative staging of esophageal cancer identifies those patients who benefit most from primary surgical treatment. Locally advanced tumor stages prompt multimodal treatment strategies. In these patients, an induction chemoradiotherapy before surgery results in a complete response in a substantial number of patients, leading to a better prognosis.[2,11] EUS, especially in combination with fine-needle aspiration (FNA), is the most accurate method for assessing the locoregional extent of esophageal carcinomas.[6,14–16,30] EUS staging has been found to significantly alter the management strategy of patients with esophageal cancer with increased referral for nonsurgical palliation.[17]

However, one limitation of conventional EUS is the inability to pass stenotic tumors making the complete assessment by conventional EUS probes impossible. Tumor stenosis not traversable for the conventional EUS probe is a common feature in esophageal carcinoma and was observed in almost 60% of the patients in our study. Although initial studies have shown that the T staging accuracy of EUS was only slightly lower for nontraversable cancer than for traversable cancer,[18,19] more recent studies showed a significantly lower staging accuracy in nontraversable tumors.[7,12,13,20] Dilatation of malignant strictures to allow more accurate staging was initially associated with perforation rates as high as 24%; although, more recently, stepwise dilatation has been shown to allow the passage of the conventional EUS probe in 85% of patients without complications.[21] In our study, using conventional EUS or miniprobe EUS depending on the grade of tumor stenosis, 100% of patients could be safely staged without time- and cost-consuming dilatation.

After our EUS algorithm, 58.8% of the patients had a stenotic tumor and were examined by miniprobe EUS, whereas the remainder could be examined by conventional EUS. This algorithm provided an overall staging accuracy of 73.2% for T stage and 74.2% for N stage, which is within but at the lower level of the range reported in the literature.[5–10] In this regard, it is important to keep in mind that EUS staging is observer-dependent with learning curves improving staging accuracy with higher case load.[22,23] Although all EUS procedures in our study were conducted by one single examiner (D.T.), we

Table 2 Overall Staging Results for N Stage (n=97), EUS Staging (uN) vs Pathohistological Staging (pN)

	pN negative	pN positive
uN negative	23	10
uN positive	15	49

Pathohistological stages pN1 and pN2 were combined to pN positive. Accuracy=74.2% (64.3–82.6), overstaging=15.5% (8.9–24.2), understaging=10.3% (5.1–18.1), sensitivity=83.1% (71.0–91.6), specificity=60.5% (43.4–76.0), positive predictive value=76.6% (64.3–86.2), negative predictive value=69.7% (51.3–84.4).
95% confidence interval given in parentheses.

Table 3 Factors Influencing Staging Accuracy

	n	T accuracy (%)	OS	US	*P*	N accuracy (%)	OS	US	*P*
Overall	97	73.2 (63.2–81.7)	13.4 (7.3–21.8)	13.4 (7.3–21.8)		74.2 (64.3–82.6)	15.5 (8.9–24.2)	10.3 (5.1–18.1)	
pT0	2	0.0 (0.0–84.2)	100 (15.8–100.0)	0.0 (0.0–84.2)					
pT1	19	68.4 (43.5–87.4)	31.6 (12.6–56.6)	0.0 (0.0–17.6)					
pT2	22	72.7 (49.8–89.3)	22.7 (7.8–45.4)	4.5 (0.1–22.8)					
pT3	54	77.8 (64.4–88.0)	0.0 (0.0–6.6)	22.2 (12.0–35.6)	0.099				
Conventional probe EUS	40	70.0 (53.5–83.4)	15.0 (5.7–29.8)	15.0 (5.7–29.8)		80.0 (64.4–90.9)	12.5 (4.2–26.8)	7.5 (1.6–20.4)	
Miniprobe EUS	57	75.4 (62.2–85.9)	12.3 (5.1–23.7)	12.3 (5.1–23.7)	0.64	68.4 (54.8–80.1)	19.3 (10.0–31.9)	12.3 (5.1–23.7)	0.25
Traversable by endoscopy	85	71.8 (61.0–81.0)	14.1 (7.5–23.4)	14.1 (7.5–23.4)		71.8 (61.0–81.0)	16.5 (9.3–26.1)	11.8 (5.8–20.6)	
Not traversable by endoscopy	12	83.3 (51.6–97.9)	8.3 (0.2–38.5)	8.3 (0.2–38.5)	0.51	91.7 (61.5–99.8)	8.3 (0.2–38.5)	0.0 (0.0–26.5)	0.18
Squamous cell cancer	28	67.9 (47.6–84.1)	21.4 (8.3–41.0)	10.7 (2.3–28.2)		75.0 (55.1–89.3)	21.4 (8.3–41.0)	3.6 (0.1–18.3)	
Adenocarcinoma	69	73.9 (61.9–83.7)	11.6 (5.1–21.6)	14.5 (7.2–25.0)	0.62	73.9 (61.9–83.7)	13.0 (6.1–23.3)	13.0 (6.1–23.3)	1
Esophagus	79	69.6 (58.2–79.5)	15.2 (8.1–25.0)	15.2 (8.1–25.0)		73.4 (62.3–82.7)	17.7 (10.0–27.9)	8.9 (3.6–17.4)	
Gastroesophageal junction	18	88.9 (65.3–98.6)	5.6 (0.1–27.3)	5.6 (0.1–27.3)	0.14	77.8 (52.4–93.6)	5.6 (0.1–27.3)	16.7 (3.6–41.4)	1
<5 cm tumor length	52	69.2 (54.9–81.3)	17.3 (8.2–30.3)	13.5 (5.6–25.8)		71.2 (56.9–82.9)	15.4 (6.9–28.1)	13.5 (5.6–25.8)	
>5 cm tumor length	35	77.1 (59.9–89.6)	8.6 (1.8–23.1)	14.3 (4.8–30.3)	0.47	77.1 (59.9–89.6)	14.3 (4.8–30.3)	8.6 (1.8–23.1)	0.62
Patients 1–49	49	63.3 (48.3–76.6)	18.4 (8.8–32.0)	18.4 (8.8–32.0)		69.4 (54.6–81.7)	18.4 (8.8–32.0)	12.2 (4.6–24.8)	
Patients 50–97	48	83.3 (69.8–92.5)	8.3 (2.3–20.0)	8.3 (2.3–20.0)	0.038	79.2 (65.0–89.5)	12.5 (4.7–25.2)	8.3 (2.3–20.0)	0.35

For each feature, staging accuracy, overstaging (*OS*), understaging (*US*), and *P* value are given for the T and N stages.
95% confidence intervals given in parentheses

demonstrated a significant learning curve for T staging accuracy, reaching 83.3% in the second half of the study vs 63.3% in the first half. This underlines the need for excellent training of the examiner, and of a sufficient case load, to achieve valid staging accuracies. Furthermore, initial reports might have overestimated the staging accuracy of EUS as recent studies reported somewhat lower accuracies than early reports.[24,25] This is a phenomenon well-known from other novel techniques being introduced into clinical practice. Possible reasons for this

Table 4 Traversability for Conventional Probe, Endoscopic Traversability, and Tumor Length as Diagnostic Tests for Differentiation of T0–2 vs T3 and N Negative vs N Positive Compared to EUS Accuracies

	T0–2 vs T3 accuracy	*P*	N accuracy	*P*
EUS	82.5 (73.4–89.4)		74.2 (64.3–82.6)	
Traversability for conventional probe	47.4 (37.2–57.8)	0	51.5 (41.2–61.8)	0.002
Endoscopic traversability	52.6 (42.2–62.8)	0.00001	44.3 (34.2–54.8)	0.00004
Tumor length	71.3 (60.6–80.5)	0.08	62.1 (51.0–72.3)	0.08

P values vs EUS accuracy are given. 95% confidence intervals given in parentheses. T and N staging accuracy of the test using tumor length was not significantly lower than EUS accuracy

observation are a publication bias favoring the novel technique, and an institutional bias, with centers of excellence publishing studies on EUS results that cannot be obtained in clinical routine use.[24]

For clinical decisions, differentiation of locally advanced vs locally limited cancer is of greater importance than the accuracy values for single T stages. In our study, the differentiation of T1–2/N negative vs T3–4 and/or N positive was correct in 84.5% of the patients. As this differentiation triggers the decision of primary surgery vs neoadjuvant therapy, we can clearly demonstrate that the use of either conventional probe or miniprobe for the staging of esophageal cancer provides adequate patient selection for the different treatment strategies.

An important finding of the present study is that conventional probe EUS (in nonstenotic tumors) and miniprobe EUS (in stenotic tumors) provided comparable accuracies for T and N staging. The conventional probe and miniprobe reached 70.0% and 75.4% T staging accuracy (P=0.64), respectively. N staging accuracy was only slightly lower for the miniprobe (68.4%) compared to the conventional probe (80.0%), this difference not reaching significance (P=0.25). It is important to note that the distribution of T and N stages were similar in both groups (conventional probe vs miniprobe), thus making the staging performances comparable. Therefore, in our opinion, a dilatation therapy of stenotic cancers to allow a conventional EUS is clearly contraindicated.

However, our study does not allow a direct comparison between the two types of EUS probes regarding staging accuracy, as they were used in different settings (miniprobe in stenotic tumors, conventional probe in nonstenotic tumors). In a previous study, a blinded comparison between the two probes including 53 patients and comparing miniprobe and conventional probe showed a superior T staging accuracy for the miniprobe compared to the conventional probe (86.8% vs 62%), [26] whereas N staging accuracies were comparable. The reported T staging accuracy for the conventional probe was markedly lower than in the actual study and might have been underestimated in the previous study.

The EUS miniprobe with a much smaller diameter and higher frequency than the conventional EUS probe is technically limited by its range and might be unable to fully image large tumors or regional lymph node involvement.[10] Previous reports showed an inferior N staging accuracy for the miniprobe compared to the conventional large diameter probe.[27] In contrast to these reports, our data show that the miniprobe is comparable to the conventional probe in detecting locally advanced stages (T3 tumors, N positive), the latter triggering neoadjuvant treatment protocols as discussed above. Our experience is that usually at least peritumoral lymph nodes can be visualized by the miniprobe EUS. The status of these lymph nodes seems to be sufficient to predict the nodal status of the patient, even if distant lymph nodes cannot be visualized.

Using a miniprobe, a differentiation of T3 vs T4 is impossible in many cases. In the clinical setting, this insufficiency to detect T4 tumors is compensated by CT scan and bronchoscopy, which detect infiltration of adjacent organs.

No T4 tumors were included in this study, although the T stage of those tumors could be accurately assessed surgically and compared to the EUS stage, even if resection was incomplete. As the preoperative diagnosis of a T4 tumor usually triggers a nonsurgical treatment, e.g., stent placement, radiotherapy, or chemotherapy, only two patients with T4 tumors underwent surgery during the study period. These two patients were falsely diagnosed as uT3 tumors preoperatively, and the T4 stages became obvious during surgery. During the study period, we identified 20 patients with T4 tumors who did not undergo surgery, and therefore could not be included in the study. We decided not to include the two falsely diagnosed patients with T4 tumors finally undergoing surgery because the exclusion of the 20 patients presumably being correctly diagnosed as T4 would have introduced a bias into this study.

The miniprobe proved to be superior to the conventional probe in differentiating early cancers in previous studies.[28,29] Because of the small proportion of T1 tumors in our study (19.6%), this did not translate into a better staging accuracy of the miniprobe in our data.

We are aware that the exclusion of patients with induction therapy, and therefore excluding advanced stages, might introduce a selection bias into our study. This bias might favor the miniprobe, as advanced stages are suspected to be less accurately staged using the miniprobe. However, in our study, the majority of patients (55.7%) had advanced T3 tumors, and no significant influence of T stage on staging accuracy for either probe was observed.

Despite the adequate staging accuracies using the miniprobe in stenotic tumors without dilatation, we have to keep in mind that FNA of suspicious lymph nodes is impossible with the miniprobe. In this regard, it has been shown in recent years that a combination of EUS with FNA can further improve lymph node staging in terms of accuracy, sensitivity, and specificity without leading to a relevant additional morbidity.[30] FNA has greatest efficacy in confirming celiac axis lymph node metastases in esophageal cancer with more than 90% accuracy.[16] As the status of these lymph nodes can determine operability, FNA is of great value for the evaluation of suspicious lymph nodes at this location.

However, one has to consider that in the present study the miniprobe was only used for tumors not being traversable for the conventional probe. In our opinion, the

possible additional information of FNA does not outweigh the risks associated with the dilatation therapy. Therefore, we advocate the safe use of the miniprobe in stenotic tumors without dilatation therapy, as our data show that this procedure offers sufficient staging accuracy for further therapy decisions.

A recent study identified tumor length (>5 cm) as an important factor influencing the accuracy of EUS for staging of esophageal cancer.[8] Most patients with tumors longer than 5 cm were understaged, and the authors believe that small areas with deeper tumor invasion might be missed in longer tumors.[8] A pull-through of the conventional probe through a stenosis with a sudden pop-up is speculated to be a further reason for the inferior accuracy. In contrast, we did not find any influence of tumor-related factors including tumor length, histology (squamous cell cancer vs adenocarcinoma), tumor location (esophagus vs esophagogastric junction), and endoscopic traversability on T and N staging accuracies. We speculate that the routine use of the miniprobe in stenotic tumors avoids the problems of tumor compression and sudden pop-up mentioned above, leading to accurate staging even in long or highly stenotic tumors.

For tumors located at the gastroesophageal junction (Siewert classification: type II), inferior staging accuracies compared to esophageal tumors have been reported.[8,15] One possible reason for this finding is the anatomically complex region with its curved area between the esophagus and stomach making the exact depth of tumor invasion more difficult to measure.[8] In the present study, we did not find a deterioration of staging accuracy for tumors of the esophagogastric junction. However, a proportion of less than 20% of tumors in this location in our study does not allow any definite conclusion regarding staging accuracy for this location.

It is well-known that endoscopic aspects offer important hints on the actual tumor stage. It has been shown previously that both tumor length >5 cm and a stenosis preventing the passage of an endoscope were likely to be associated with a T3 stage or higher.[31] We found that tumor length predicted T stage (T1–2 vs T3) and N stage with an accuracy similar to that achieved by EUS staging. In contrast, tumor stenosis failed to predict T and N stages in our study.

Conclusion

The EUS miniprobe used in stenotic esophageal cancers and the conventional probe used in nonstenotic cancers provide the same staging accuracy for T and N stages. They allow a reliable selection of patients for neoadjuvant treatment protocols. Dilatation therapy to allow the passage of a conventional EUS probe, carrying a significant risk of esophageal perforation, should therefore be avoided.

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Duodenojejunostomy Leaks After Pancreaticoduodenectomy

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Abstract
Background A duodenojejunostomy (DJ) or gastrojejunostomy (GJ) leak is a potentially fatal complication after pancreaticoduodenectomy (PD). However, due to its rarity, this complication has not been fully characterized.
Methods We reviewed 3029 PDs performed at our institution over a 26-year period and identified patients who suffered a leak at the DJ or GJ anastomosis. Perioperative data from patients with such a leak were examined in detail and were compared to patients who did not experience such a leak after PD.
Results A total of 13 patients experienced a DJ or GJ leak after PD, amounting to a 0.4% leak rate. Common clinical signs of a leak included an acute abdomen, enterocutaneous fistula, and a fever. Twelve of thirteen patients also had a leukocytosis, with five patients having a peak white blood cell count exceeding 30,000 cells/mm^3. The median time interval between surgery and diagnosis of the DJ or GJ leak was 10 days; three patients were diagnosed after being discharged from the hospital and one patient was diagnosed on the day of their planned discharge. In a multivariate model, perioperative risk factors for a DJ or GJ leak included a preoperative BUN-to-creatinine ratio>20 (odds ratio=6, p=0.01), intraoperative blood loss ≥1 l (odds ratio=6, p=0.03), and a total pancreatectomy (odds ratio=7, p=0.005). In the DJ or GJ leak group, 12 of 13 patients were managed operatively. The median postoperative length of stay was 35 days after PD, and four patients died within 4 months of surgery as a result of their complicated postoperative course.
Conclusion DJ or GJ leaks occur infrequently after PD, but are associated with substantial morbidity. The clinical presentation is usually delayed, and surgical management is the preferred approach. Early diagnosis, attention to preoperative volume status, and continued efforts to control blood loss may minimize the impact of DJ or GJ leaks in some instances.

Keywords Pancreaticoduodenectomy · Whipple · DJ leak · GJ leak

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Introduction

Pancreaticoduodenectomy (PD) is a complex gastrointestinal operation performed for both benign and malignant disease of the pancreatic head and periampullary region. The reconstruction of the gastrointestinal tract after removal of the specimen typically involves three anastomoses to a jejunal limb: a pancreaticojejunostomy (PJ), an hepaticojejunostomy (HJ), and a duodenojejunostomy (DJ) in the instances when the pylorus is preserved. A gastrojejunostomy (GJ) is performed when the pylorus is not preserved.

PD has an associated complication rate of approximately 40%, with substantial morbidity directly related to poor anastomotic healing.[1–3] Leaks from the PJ occur in approximately 10% of patients undergoing PD.[3,4] Bile leaks are less common, occurring in 3% of the cases.[3]

The incidence of DJ or GJ leaks after PD is not known, but is believed to occur less often than leaks at the other two anastomoses. Most large series of PDs do not report the DJ or GJ leak rate either because the complication was never encountered, or more likely because the complication was not prospectively tracked. To better characterize DJ or GJ leaks after PD, we identified 13 patients in our PD series that suffered such a leak and studied their hospital courses in detail. This study establishes the frequency, clinical presentation, appropriate management, and clinical implications of this unusual complication after PD.

Materials and Methods

Perioperative data were reviewed for the patients who underwent a PD at the Johns Hopkins Hospital between 1981 and March of 2007. A total of 36 surgeons performed 3,154 PDs during this time period, although 78% of these were performed by three surgeons (KDL, CJY, and JLC). We excluded 125 patients from the analysis because of inadequate data. The study was approved by the IRB.

Surgical Technique

Relevant technical aspects of a PD are reviewed below, while more detailed descriptions of the operation are provided elsewhere.[3,5,6] The majority of the PDs in this series were pylorus preserving with a standard lymph node harvest. A distal gastrectomy was performed in the early years of the experience, or when there was a question of ischemia or tumor involvement of the proximal duodenum. Vagotomy, tube gastrostomy, and feeding jejunostomy were not routinely performed. After removing the specimen, gastrointestinal reconstruction was typically performed with the jejunal limb placed in the retrocolic position. Generally, the PJ was constructed first, followed by the HJ, and DJ (or GJ when a distal gastrectomy was performed). The DJ or GJ was most commonly performed in two layers: an inner continuous layer with 3–0 Vicryl and an outer interrupted layer with 3–0 silk. One or more 10-mm Jackson-Pratt® silicone drains (CardinalHealth, Dublin, OH) were left in the vicinity of the PJ and HJ anastomoses, and brought out of the abdomen though separate stab incisions. Postoperative management for uncomplicated cases followed the Johns Hopkins Hospital critical pathway for PD, as described elsewhere.[7]

Statistical Analysis

A DJ or GJ leak was defined in this study as conclusive radiographic or direct visual evidence of a defect at the DJ or GJ. Statistical comparisons were made in this study between patients with and without such leaks following PD. Relevant perioperative data included patient demographics, preoperative laboratory data, intraoperative data, pathologic features, postoperative complications, postoperative length of stay, and long-term survival. In analyses of preoperative laboratory tests, the values were collapsed into categorical variables using the 75th percentile value for the study population as a cutoff value for each individual test (i.e., a value was categorized as either above or below the cutoff value). Postoperative mortality is defined here as mortality within 30 days of the PD or during the index hospitalization. Surgery-related mortality was presumed for deaths that occurred within 4 months of the PD, as several patients in the DJ or GJ group clearly died from complications of their leak, yet the deaths were not accounted for using the traditional definition for perioperative mortality. Definitions of specific postoperative complications such as pancreatic fistula and delayed gastric emptying appear elsewhere.[8,9]

The Clavien complication grading system was used to estimate complication severity in patients with DJ or GJ leaks after PD. This model has been described in detail by the authors of the grading system.[10] Briefly, the classification system uses a six-tiered approach (Grades 0 through Grade 5) that is based on the invasiveness of the interventions used to manage the complications. Grade 0 indicates that there are no complications and no deviations from the critical pathway. Grades I and II complications are managed with pharmacologic agents or other noninvasive measures; Grade IIIa complications are managed with invasive procedures but do not employ general anesthesia; Grade IIIb complications are managed with invasive procedures plus general anesthesia; Grade IVa complications involve intensive care unit management for single organ dysfunction; Grade IVb complications involve intensive care unit management for multiorgan dysfunction; and Grade V complications indicate perioperative death. Complications in the highest three categories (III–V) are considered to be "severe" complications for the purposes of this study.

Comparisons of continuous variables were performed using the Mann–Whitney ranksum test and comparisons of categorical variables were performed using a Chi-squared test or simple logistic regression. Multivariate logistic regression was used to determine clinical predictors of a DJ or GJ leak. Long-term survival data were compared using the Kaplan-Meier method and log rank test. Median values are used to summarize distributions when appropriate.

Although 3,029 patients were included in the study, sample sizes for specific perioperative variables deviated

slightly from this number reflecting partial completeness of certain datasets. For instance, some patients had preoperative laboratory testing performed at an outside institution and therefore did not have preoperative laboratory results in our database. Statistical significance was accepted for $p<0.05$. The data analyses were performed using Intercooled Stata Version 8.2 (Chicago, IL).

Results

Incidence of DJ or GJ Leak Rate After PD

There were 13 out of 3,029 patients who suffered a DJ or GJ leak after PD, resulting in a 0.4% leak rate for the series. DJ or GJ leaks were not clustered early in the series, but rather occurred at a consistent rate over time (linear regression, $p=0.6$). Eleven of the thirteen patients had a pylorus preserving operation, whereas two patients also had a distal gastrectomy performed in conjuction with their PD.

Clinical Presentation of DJ or GJ Leaks After PD

The postoperative courses of patients who suffered DJ or GJ leaks were studied in detail to characterize the clinical presentation of this infrequent complication (Table 1). The most common clinical signs of a DJ or GJ leak following a PD included an acute abdomen, enterocutaneous fistula, and fever. Radiographic support for a DJ or GJ leak was usually present, and included free air on X-ray or computed tomography, or extravasation of contrast on a sinogram or upper gastrointestinal series. Eleven of twelve patients with available postoperative laboratory data experienced a leukocytosis around the time of diagnosis, and five of the patients had white blood cell counts exceeding 30,000 cells/mm^3. Typically, patients presented with symptoms related to their DJ or GJ leak on postoperative day 10. The earliest presentation in this series occurred on the sixth postoperative day, and the most delayed presentation occurred on the 20th postoperative day. One patient developed symptoms on the day they were to be discharged from the hospital, and three patients developed symptoms after they were discharged from the hospital in good condition.

Pre- and Intraoperative Risk Factors

We compared pre- and intraoperative data between patients with ($n=13$) and without ($n=3016$) a DJ or GJ leak after PD to identify risk factors for such a leak (Table 2). Patient demographics were similar between the two groups. Results of routine preoperative laboratory tests, such as the components of the comprehensive metabolic and hematologic panels, were also similar (data not shown) with the exception of the serum blood urea nitrogen (BUN). An increased proportion of patients in the DJ or GJ leak group had preoperative BUN levels of 18 mg/dl or more (55 vs 27%, $p=0.04$). The difference between the two groups was magnified when the preoperative serum creatinine was also factored; 70% of the patients with a DJ or GJ leak had a preoperative BUN-to-creatinine ratio>20, as compared to 26% of patients without a DJ or GJ leak ($p=0.002$). A greater proportion of patients in the leak group had a low preoperative albumin (≤3.5 g/dl), although this difference was not significant (42 vs 26%, $p=0.2$).

Patients in the DJ or GJ leak group generally had more complicated intraoperative courses than patients without such leaks. For instance, patients with a leak had more blood loss (median, 1,500 vs 700 ml, $p<0.001$) and a higher transfusion rate (69% vs 39%, $p=0.02$). In addition, the operations were longer by more than 1 h (median, 430 vs 369 min, $p=0.06$), although this last comparison

Table 1 Clinical Presentation of a DJ or GJ Leak After PD

Patient	Clinical signs	Imaging findings	Peak WBC before diagnosis (cells/mm^3)	Postoperative day at diagnosis
1	EC fistula	No study	Not available	20
2	Fever	GJ leak on UGI	44	8
3	EC fistula	No study	32	14
4	Fever	Positive sinonogram	22	12
5	Acute abdomen	Pneumoperitoneum	19	6
6	Fever	DJ leak on UGI	26	13
7	Acute abdomen	Pneumoperitoneum	24	9
8	Acute abdomen	Pneumoperitoneum	19	9
9	No symptoms	Pneumoperitoneum	38	12
10	Acute abdomen	Pneumoperitoneum	41	10
11	No symptoms	Pneumoperitoneum	43	9
12	Acute abdomen	No study	27	11
13	Acute abdomen	No study	8	9
	Median (range)		27 (8–44)	10 (6–20)

EC enterocutaneous, *UGI* upper gastrointestinal contrast study

Table 2 Pre- and Intraoperative Data in Patients With and Without a DJ or GJ Leak

	DJ or GJ leak, n=13	No DJ or GJ leak, n=3,016	P value
Demographic data			
Age, years, median (range)	66 (22–85)	65 (15–103)	0.4
Male, n (%)	6 (46)	1,608 (53)	0.6
Caucasian, n (%)	12 (92)	2,627 (87)	0.6
Preoperative laboratories			
Albumin, ≤3.5 g/dL, n (%)	5 (42)	696 (26)	0.2
BUN/Cr, ≥21, n (%)	7 (70)	691 (26)	0.002
Intraoperative data			
EBL, ml, median (range)	1,500 (400–4,500)	700 (50–2,800)	0.008
Blood transfusion, n (%)	9 (69)	1,038 (37)	0.01
Operative time, min, median (range)	430 (275–660)	369 (56–1,170)	0.06
Total pancreatectomy, *n* (%)	4 (31)	138 (5)	<0.001
Major visceral vessel resected, *n* (%)	0 (0)	92 (3.1)	0.6
Pylorus sparing, *n* (%)	11 (85)	2,325 (77)	0.5

DJ duodenojejunostomy, *GJ* gastrojejunostomy, *BUN* blood urea nitrogen, *Cr* creatinine, *EBL* estimated blood loss

narrowly missed statistical significance. Total pancreatectomy was more common in the leak group (31 vs 5%, $p<0.001$). No difference was observed between the groups in the proportion of patients who underwent a pylorus preserving operation (85 vs 77%, $p=0.5$). The proportions of specimens harboring invasive cancer were comparable in the two groups (77 vs 74%, $p=0.8$), and no specific pathology proved to be a risk factor for a DJ or GJ leak.

Three univaratiate risk factors proved to be significant in a multivariate logistic regression model. These included a preoperative BUN-to-creatinine ratio>20 (odds ratio for a DJ or GJ leak=6, $p=0.01$), ≥1 l blood loss (odds ratio=6, $p=0.03$), and total pancreatectomy (odds ratio=7, $p=0.005$).

Postoperative Data

Surgical outcome data in the two groups of patients are summarized in Table 3. The control group of patients without a DJ or GJ leak had a mortality and morbidity rate of 2 and 44%, respectively. The reoperation rate was 4% and the median postoperative hospital stay was 10 days. Although just one patient in the DJ or GJ leak group suffered a perioperative death according to the strict definition used in this study (death within 30 days of the operation or during the index hospitalization, 8% rate, $p=0.09$), surgery-related mortality was clearly higher. The DJ or GJ leak was a principle factor contributing to the demise of four additional patients who died within 4 months of their PD. In one instance, the patient was readmitted with symptoms of a GJ leak shortly after discharge and died during the second hospitalization. In the other three instances, the patients died after transfer to a rehabilitation facility. The reoperation rate in the DJ or GJ leak group was 92% ($p<0.001$) and the median postoperative hospital stay was 36 days ($p<0.001$). Specific complications associated with a DJ or GJ leak included wound infection (54 vs 9% in patients without a DJ or GJ leak, $p<0.001$), bile leak (46 vs 3%, $p<0.001$), pancreatic fistula (38 vs 11%, $p=0.001$), intraabdominal abscess (38 vs 6%, $p<0.001$), and sepsis (31 vs 2%, $p<0.001$). In several instances, leaks from the

Table 3 Postoperative Data Of Patients With And Without A DJ or GJ Leak

	DJ or GJ leak, n=13	No DJ or GJ leak, n=3016	P value
Morbidity, *n* (%)	13 (100)	1,328 (44)	<0.001
Perioperative mortality, *n* (%)	1 (8)	46 (2)	<0.001
Death<4 months after PD, *n* (%)	5 (38)	147 (5)	<0.001
Reoperation, *n* (%)	12 (92)	115 (4)	<0.001
Postop hospital LOS, median (range)	35 (7–85)	10 (4–388)	<0.001
Specific complications			
Wound Infection, *n* (%)	8 (62)	279 (9)	<0.001
Bile leak, *n* (%)	6 (46)	87 (3)	<0.001
Pancreatic fistula, *n* (%)	5 (38)	318 (11)	<0.001
Intraabdominal abscess, *n* (%)	5 (38)	166 (6)	<0.001
Sepsis, *n* (%)	4 (31)	70 (2)	<0.001
DGE, *n* (%)	0 (0)	459 (15)	0.1

DJ duodenojejunostomy, *GJ* gastrojejunostomy, *Postop* postoperative, *LOS* length of stay, *DGE* delayed gastric emptying

PJ or HJ anastomoses manifested even after the DJ or GJ leak was addressed.

Complication Severity and Management

We used the Clavien complication grading system to characterize complication severity in the 13 patients with DJ or GJ leaks (Table 4). All 13 patients with such leaks after PD had "severe" complications: eight patients had grade III complications, four patients had grade IV complications, and one patient had a grade V complication.

The DJ or GJ leak was surgically managed in 12 out of the 13 patients. In two patients, the DJ was successfully revised, and in the remaining 10 patients, a distal gastrectomy with GJ was necessary. Eight patients were taken to the operating room for an exploratory laparotomy shortly after the clinical and radiographic diagnosis of an enteric leak. In four cases, unsuccessful attempts to manage the leaks nonoperatively delayed definitive management; the intervals between the diagnosis of a DJ or GJ leak and the surgical management of the leaks for these patients were 4, 7, 17, and 31 days, respectively. Successful nonoperative management of a GJ or DJ leak was performed in one patient. The hospitalization involved multiple percutaneous drainage procedures for intraabdominal abscesses, and lasted 49 days.

Survival

While surgery-related mortality was high after a DJ or GJ leak (5/13 or 38%), long-term survival did not appear to be affected by this complication. Figure 1 shows the Kaplan-Meier survival curves of patients with and without a DJ or GJ leak. The graph excludes the five patients in the DJ or GJ leak group who had a surgery-related death, as well as the patients in the control group who survived less than 4 months after their PD. In the DJ or GJ leak group, the median survival had not been reached by 16 months; the median survival was 53 months in the control group ($p=0.9$). Three patients with benign disease and a DJ or GJ leak were still alive at last follow-up (≥3.5 years after PD). Five patients with malignant disease in the DJ or GJ leak group had pancreatic cancer; two of these patients were alive at last follow-up (5 and 10 months, respectively). The former patient has begun chemotherapy.

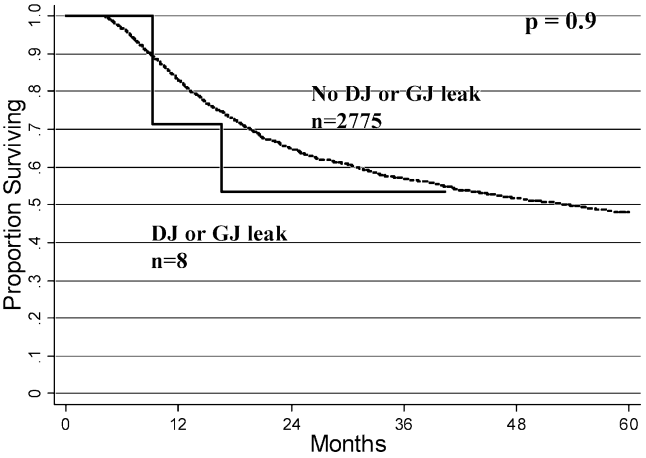

Figure 1 Kaplan-Meier survival curves for patients with and without DJ or GJ leaks. Patients who suffered a surgery-related mortality within 4 months of their PD are excluded.

Table 4 The Clavien Complication Grading System Applied To Patients With DJ or GJ Leaks After PD

Patient[a]	Clavien grade	Explanation of complication grade
1	IVb	DJ revision, renal failure, congestive heart failure
2	IIIa	Percutaneous abscess drainage
3	IIIb	Distal gastrectomy and GJ
4	IIIb	DJ revision
5	IIIb	Distal gastrectomy and GJ
6	IIIb	Distal gastrectomy and GJ
7	V	Distal gastrectomy and GJ, Death
8	IVa	Distal gastrectomy and GJ, Renal failure
9	IVa	Distal gastrectomy and GJ, renal failure
10	IIIb	Distal gastrectomy and GJ
11	IIIb	Distal gastrectomy and GJ
12	IIIb	Distal gastrectomy and GJ
13	IVa	Distal gastrectomy and GJ, hemodynamic instability

DJ duodenojejunostomy; *GJ* gastrojejunostomy
[a] Patient numbers listed here correspond to the patient numbers in Table 1

Discussion

In contrast to some of the more common complications after PD, such as delayed gastric emptying and pancreatic fistula, certain low frequency complications are poorly characterized in the surgical literature. Most institutions have not encountered these problems enough to draw any significant conclusions about them, and national databases do not track such complications. Nevertheless, some low frequency complications after PD result in substantial morbidity, and pancreatic surgeons should be aware of their clinical impact.

We reviewed our institutional experience of over 3,000 PDs and identified 13 patients who experienced a postoperative leak at the DJ or GJ anastomosis, amounting to a leak rate of 0.4%. The DJ or GJ leak rate observed in this series was comparable to the enteroenteric leak rates reported for other gastrointestinal operations, such as gastric bypass and colon surgery.[11–13] To put the DJ or GJ

leak rate observed from this series into a larger perspective, one may project that a surgical department or high-volume pancreatic surgeon who performs 20 PDs per year would encounter an average of one DJ or GJ leak every 5 years.

Three significant perioperative risk factors for a DJ or GJ leak were identified in this study: a preoperative BUN-to-creatinine ratio above 20, ≥1 l blood loss, and a total pancreatectomy. While these retrospective data are based on a small number of patients with a DJ or GJ leak and therefore subject to over interpretation, it is tempting to link these three risk factors by their similar potential to affect blood flow to the enteroenteric anastomosis. An elevated BUN-to-creatinine ratio is suggestive of preoperative hypovolemia and may be associated with an increased risk for intraoperative hypotension. Large volume blood loss may be associated with a similar outcome. Total pancreatectomy may involve the ligation of the right and left gastroepiploic arteries, and the branches of the splenic artery including the dorsal pancreatic artery, the great pancreatic artery, and the caudal pancreatic artery. These blood vessels provide collateral blood flow to pancreaticoduodenal arcades and may be important for adequate perfusion of the DJ or GJ in some patients. Technical factors were not considered in the multivariate risk model, but may have contributed to the development of DJ or GJ leaks. It is worth noting, however, that of the five surgeons who performed the 13 PDs in the DJ or GJ leak group, four were highly experienced pancreatic surgeons accounting for over 80% of the cases in the control group.

Although impaired collateral blood flow to the DJ or GJ anastomosis may contribute to the increased leak rate in patients who underwent a total pancreatectomy, distal gastrectomy did not offset this problem. Of the four patients in the DJ or GJ leak group who had a total pancreatectomy, two had a distal gastrectomy performed. The overall enteroenteric leak rates in the entire cohort of patients who underwent a total pancreatomy (142 patients) were similar whether the pylorus was preserved (2/97 or 2%) or not (2/45 or 4%, $p=0.4$, personal communication from JMW).

A pylorus preserving operation was more commonly performed in the DJ or GJ leak group (11 of 13, or 85%), but univariate and multivariate analysis did not identify this technical factor to be a significant contributor to the development of a DJ or a GJ leak. Indeed, pylorus preservation was also performed in the majority of the patients in the control group (2,325 of 3,009, or 77%) who did not experience such a leak. The proportions of patients in which the pylorus was preserved was not significantly different between the two groups ($p=0.5$).

DJ or GJ leaks typically manifested on or after the tenth postoperative day. Since the median postoperative length of stay for the control group without a DJ or GJ leak was 10 days (and even shorter in our recent experience),[2] this complication may easily be missed before the patient leaves the hospital. In fact, one patient from this series presented on the day of their planned discharged, and three patients presented after their discharge. In retrospect, subtle clues of a DJ or GJ leak may have been present prior to the definitive diagnoses; however, abnormal signs or symptoms were likely to have been attributed to the more common complications following PD in these patients, such as a pancreatic fistula or a bile leak. For instance, the patient diagnosed with a high output enterocutaneous fistula on the 20th postoperative day developed a wound infection a few days prior to the diagnosis. Around the time when the wound infection was appreciated, a CT scan was performed which showed that the jejunal limb was positioned in close proximity to the open abdominal wound.

DJ or GJ leaks were managed operatively in 12 of 13 patients. The single patient who was managed nonoperatively required multiple percutaneous interventions to control intraabdominal abscesses and had a longer postoperative course than six patients who underwent second operations. Two surgically managed patients underwent local repair of a disrupted DJ, and the ten remaining patients underwent a distal gastrectomy with GJ.

Although DJ or GJ leaks occurred infrequently in this series, they always had a profound impact on the postoperative course. According to the Clavien criteria, the complications were considered "severe" in all 13 patients. This differed from our experience with pancreatic fistulas, where roughly 25% were considered "severe."[7] Only three patients had a postoperative length of stay fewer than 23 days; the postoperative lengths of stay in the exceptional cases do not accurately reflect the morbidity of the leaks in these patients since they were discharged before the complication was even diagnosed. One patient died in the hospital after readmission, and the other two patients had long hospital stays after they were readmitted (22 and 57 days, respectively). DJ or GJ leaks were associated with an increased reoperation rate and increased risk of other complications (e.g., wound infection, bile leak, pancreatic fistula, intraabdominal abscess, and sepsis). Most importantly, 5 of 13 patients (38%) had a surgery-related death within 4 months of their PD.

Despite the severe consequences of a DJ or GJ leak, the survival data from this study demonstrate that successful management of this complication is possible. Patients can recover and achieve long-term survival that is comparable to the survival observed in patients without such a leak. The initiation of chemotherapy in one patient with pancreatic cancer highlights that a full recovery is possible after a DJ or GJ leak. An awareness of the signs and symptoms, as well as the appropriate management, is imperative for optimal results.

Conclusion

DJ or GJ leaks are infrequent events after PD, but are virtually always associated with severe patient morbidity. When they occur, the risk of a surgery-related death is high. Typically, DJ or GJ leaks manifest clinically at least 1 week after surgery. The causes of this unusual complication are not known but may be related to impaired perfusion of the anastomosis. Surgery is usually the preferred management strategy.

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Preoperative Predictors for Complications after Pancreaticoduodenectomy: Impact of BMI and Body Fat Distribution

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Abstract
Background The purpose of this study was to examine the preoperative patient and radiographic factors that are associated with operative morbidity after pancreaticoduodenectomy.
Material and Methods Patient characteristics and preoperative radiographic findings and their association with postoperative complications after pancreaticoduodenectomy were analyzed for 356 patients with pancreatic adenocarcinoma who underwent resection between 2000 and 2005.
Results Postoperative complications developed in 135 patients (38%). The most common complications were pancreatic fistula/abscess (15%), wound infection (14%), and delayed gastric emptying (4%). On multivariate analysis, the only preoperative radiographic factors associated with having any postoperative complication were the absence of pancreatic atrophy and the extent of central obesity determined by the thickness of retrorenal visceral fat (VF). Complications occurred in 51% of patients with VF≥2 cm, compared to 31% of patients with VF<2 cm, $p<0.001$. Postoperatively, pancreatic fistula developed in 24% of patients with VF≥2 cm and in only 10% of patients with VF<2 cm, $p=0.01$. Wound infections occurred in 21% of the patients with body mass index greater than or equal to 30 kg/m^2 compared to 12% of the nonobese patients, $p=0.03$.
Conclusions Generalized obesity is associated with postoperative wound infections after pancreaticoduodenectomy. The degree of visceral fat on preoperative cross-sectional imaging is associated with significantly higher rates of overall complications and pancreatic fistula.

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Keywords Pancreaticoduodenectomy · Complications · Obesity

Introduction

Improvements in the pre-, peri-, and postoperative management of patients undergoing pancreaticoduodenectomy along with an appreciation for appropriate patient selection have reduced operative mortality rates to less than 3% in most medical centers.[1] Despite this substantial decline in operative mortality over the past two decades, postoperative complications occur in approximately 40% of patients after pancreaticoduodenectomy.[1–5] Even high-volume centers with vast experience in pancreatic surgery report major complications requiring prolonged hospital stay and invasive intervention in approximately 20% of patients undergoing pancreaticoduodenectomy.[1,3,5–7] When studied in a prospective manner, technical and pharmacologic efforts to reduce the incidence of major complications after pancreaticoduodenectomy namely, pancreatic fistula and delayed gastric emptying (DGE), have not been shown to significantly reduce this postoperative morbidity.[8–12] Retrospective reviews of large, single-institution pancreatic surgery databases have identified few risk factors, whether patient, surgeon, or disease related, for major postoperative complications after pancreaticoduodenectomy.[3,4,13–15]

Historically, the patient-related factors that were considered preoperatively to increase surgical complication rates and mortality after pancreaticoduodenectomy were active alcoholism, coagulopathy, severe jaundice, acute renal failure, heart disease, and obesity.[16,17] More recently, preoperative biochemical markers reflective of potential protein–calorie malnutrition or uncharacterized azotemia have been associated with postoperative morbidity after pancreaticoduodenectomy.[18] Because of the growing prevalence of obesity in the US population over the past three decades, surgeons have acquired appreciation for generalized extreme obesity as a potential risk factor for operative morbidity and mortality. Extreme obesity is an established risk factor for postoperative morbidity after many nonbariatric operations, including orthopedic, cardiac, gynecologic, and reconstructive procedures; however, few studies have addressed the direct impact of obesity and body fat distribution on postoperative complications after pancreaticoduodenectomy.[16,19,20]

The purpose of this study was to examine whether comorbid diseases, including obesity, and preoperative cross-sectional radiographic findings in patients with pancreatic adenocarcinoma are associated with a greater likelihood of complications after pancreaticoduodenectomy.

Material and Methods

Patients and Complications

The study population consisted of 356 consecutive patients who underwent pancreaticoduodenectomy for pancreatic adenocarcinoma at the Memorial Sloan-Kettering Cancer Center (MSKCC) between 2000 and 2005. Permission for studying these patients was obtained from the MSKCC Institutional Review and Privacy Board according to institutional policy for protected health information. All patients were identified from a prospectively maintained pancreatic cancer database containing demographic, clinical, operative, pathological, and follow-up data. Operative complication data was accessed from a prospective surgical complication database that contains standardized definitions for complications graded according to severity of morbidity. The process of entering complications relative to the operation as well as auditing for complication accuracy has been described previously for this institution.[5]

Twenty different postoperative complications were reported for the patients in this study. Pancreatic fistula, DGE, and wound infection accounted for more than 90% of all complications. A pancreatic fistula was reported when there were clinical signs and symptoms or radiologic confirmation of a pancreatic anastomotic leak with amylase-rich fluid drainage greater than or equal to 50 mL/day beyond postoperative day 5. DGE was defined by the inability to provide adequate oral hydration by postoperative day 10. Wound infection was not categorized as superficial or deep.

Preoperative Cross-sectional Imaging

Preoperative computed tomography (CT) and/or magnetic resonance abdominal imaging (MRI), acquired either at MSKCC or an outside facility, was available for all patients. Approximately one half of the patients had preoperative cross-sectional imaging performed at MSKCC, and 10% of patients had an abdominal MRI as the only modality of preoperative imaging. Preoperative scans were evaluated by a reviewer (House, Winston) blinded to the patients' postoperative outcomes. The use of radiographic measures allowed us to evaluate body fat distribution as well as pancreatic duct (PD) diameter and pancreatic atrophy.

Measurements for abdominal wall (AW) and hip girdle (HG) fat thickness, retrorenal visceral fat (VF), and PD diameter were performed according to easily reproducible guidelines (Fig. 1). AW fat thickness was measured as the paramedian vertical distance between the left rectus abdominus fascia and the skin at the level of the umbilicus. HG fat thickness was recorded as the distance between the iliac plate and skin at the level of the posterior superior iliac spine. In rare cases, only an abdominal scan was available for

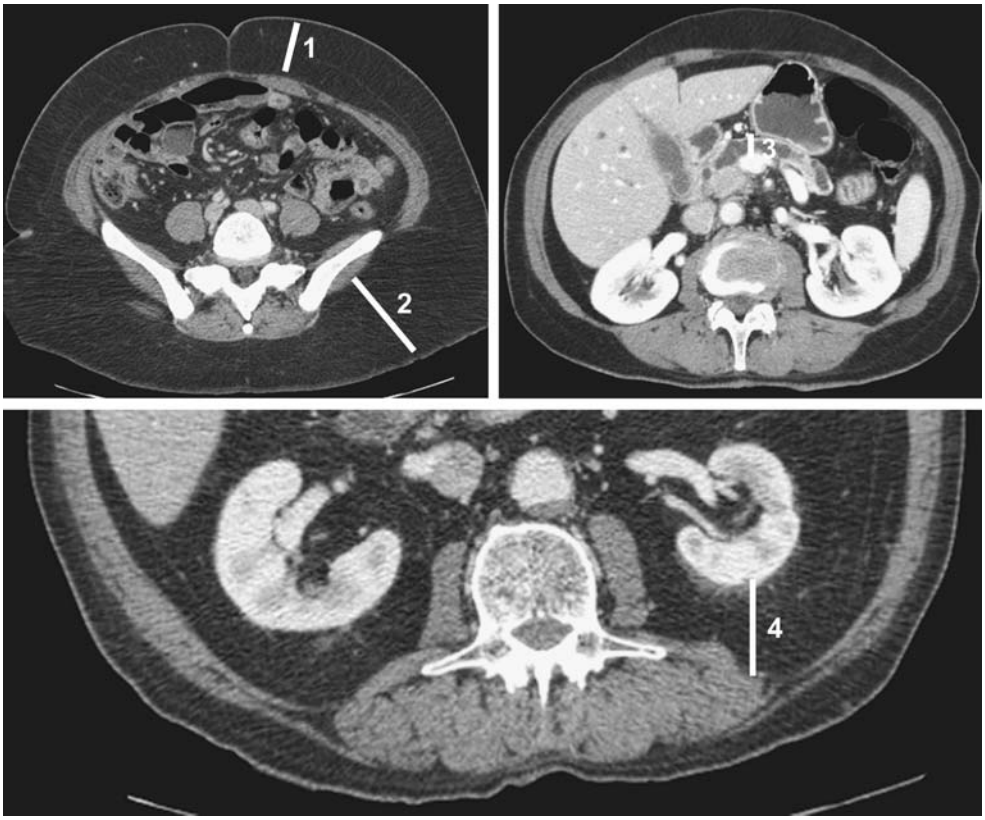

Figure 1 AW fat thickness (*1*): paramedian vertical distance between the left rectus abdominus fascia and the skin at the level of the umbilicus. HG fat thickness (*2*): distance between the iliac plate and skin at the level of the posterior superior iliac spine. PD diameter (*3*): width of the duct overlying the portal-superior mesenteric vein confluence. VF thickness (*4*): vertical distance between the left posterior renal capsule and the junction of the abdominal wall and paraspinal musculature at the level of the left renal vein.

evaluation and did not permit measurement of HG fat thickness. VF thickness was measured as the vertical distance between the left posterior renal capsule and the junction of the AW and paraspinal musculature at the level of the left renal vein. The PD diameter was measured as the width of the duct overlying the portal-superior mesenteric vein confluence.

The presence of radiographic pancreatic atrophy on preoperative CT and/or MRI was determined subjectively and recorded in a binomial fashion as present or absent.

Statistics

Statistical analyses were performed appropriately with SPSS version 12.0 for Windows (Statistical Package for the Social Sciences, Chicago, IL) and/or SAS version 9.1 (Statistical Analysis System, Cary, NC). Categorical variables were compared using a Fischer's exact test as appropriate. Continuous variables were expressed as median or mean±standard error of the mean and were compared using a two-sample *t* test. Significant univariate factors were included in a logistic regression model to determine multivariate significance.

Results

A total of 356 patients with a median age of 69 years underwent pancreaticoduodenectomy (Table 1). More than 90% of the patients were treated with a classic pancreaticoduodenectomy that included a gastric antrectomy. The remaining patients were treated with a pylorus-preserving procedure. Seventy percent of the pancreaticoduodenectomies resulted in a margin-negative R0 resection. Less than 2% of pancreaticoduodenectomies required a portal-superior mesenteric vein resection. The average pathologic tumor diameter within resected specimens was 3.0 cm, and 69% of patients were staged with positive involvement with the lymph nodes. Operative notes for each patient were reviewed and confirmed that after resection, nearly all patients were reconstructed with an end-to-side duct-to-mucosa pancreaticojejunostomy, an end-to-side hepaticojejunostomy, and an antecolic gastro(duodeno)jejunostomy. Significant differences in operative time and operative blood loss were not associated with any preoperative risk factor included in this study. As shown in Fig. 2, a linear relationship between operative time and body mass index (BMI) was not apparent. The mean operative blood loss for patients with BMI≥30 kg/m^2 was 686 vs 595 mL for patients with BMI<30; $p=0.6$.

The mean BMI for the patients in this study was 26.3 kg/m^2 (range, 15.2–47.6). Preoperative comorbid conditions are summarized for all patients in Table 1. Seventeen percent of patients carried a diagnosis of diabetes mellitus that required oral hypoglycemic agents and/or insulin injection before operation. Twenty-two percent of patients were

Table 1 Patient, Operative, and Pathologic Characteristics

Characteristics	Value
Total patients	356
Median age (range)	69±0.5 years (43–92)
Gender	
Male	171 (48%)
Female	185 (52%)
BMI[a]	26.3±0.3 kg/m^2 (15.2–47.6)
Body mass[a]	72.9±0.9 kg (35.8–140)
Medical history	
Tobacco use	79 (22%)
Alcohol abuse	70 (20%)
Diabetes mellitus	62 (17%)
Cardiac disease	82 (23%)
COPD	17 (5%)
Cancer stage	
T1	4 (1%)
T2	8 (2%)
T3	344 (97%)
Node-positive	246 (69%)
Tumor diameter[a]	3.0±0.1 cm (0–6.5)
Operation	
Pylorus-preserving	33 (9%)
Classic	323 (91%)
Operative blood loss[a]	612±29 ml (100–4,000)
Complications[b]	
Any complication	135 (38%)
Pancreatic fistula	54 (15%)
Wound infection	49 (14%)
Delayed gastric emptying	14 (4%)
LOS[a] ($p<0.001$)	13±0.5 days (2–72)
Without complications	10±0.3 days (4–45)
With complications	17±1.0 days (2–72)
30-day mortality	6 (1.7%)
90-day mortality ($p=0.03$)	14 (4%)

[a] Expressed as mean±SEM (range)
[b] Other complications (<2%): GI bleeding, cholangitis, pneumonia, urinary tract infection, cardiac ischemia/arrythmia, bowel obstruction, line sepsis, and venous thrombosis

current smokers within 1 month of the time of initial preoperative surgical evaluation, and 20% of patients reported a past history of heavy alcohol consumption. We were not able to determine accurately the number of patients who were either jaundiced or treated with preoperative biliary stenting before pancreaticoduodenectomy.

Postoperative complications were reported in 135 (38%) patients. For patients who developed a postoperative complication, multiple complications were reported in 44 (33%) patients. In descending order, the four most frequent complications were pancreatic fistula (15%), wound infection (14%), DGE (4%), and cardiac ischemia/dysrrhythmia (3%). Wound infections and DGE were observed in 8 (15%) and 14 (26%) of the 54 patients with a postoperative pancreatic fistula, respectively. DGE was only recorded in patients who developed a pancreatic fistula. There was no difference in the incidence of wound infections for patients with or without a postoperative pancreatic fistula.

The 30- and 90-day mortality for patients in this study was 1.7 and 4%, respectively. The 90-day mortality for patients who developed a complication after pancreaticoduodenectomy was significantly higher than that for patients free of postoperative complications, 8 vs 1.4%; $p=0.03$. Three patients without postoperative complications died of rapidly progressive metastatic disease within 3 months of pancreaticoduodenectomy. The mean postoperative hospital length of stay was 13 days (range, 2–72 days) for all patients in this study.

Differences in BMI and Body Fat Distribution For Patients with Complications

The mean body mass for all patients was 73 kg. As shown in Table 2, there was a significant difference in total body mass and BMI for patients who developed a postoperative wound infection. BMI was not significantly higher for patients with any other postoperative complication after pancreaticoduodenectomy. Radiologic measurements of anterior AW and HG thickness on preoperative cross-sectional imaging did not differ significantly among patients who did or did not develop a postoperative

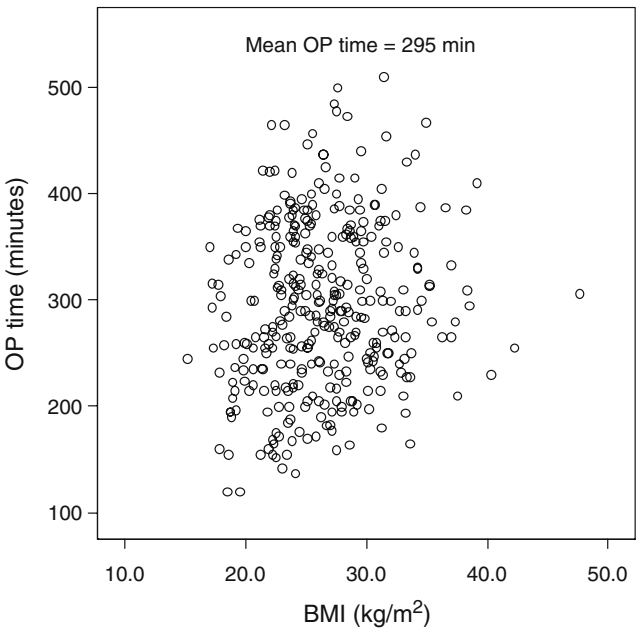

Figure 2 Relationship between operative time (*OP time*) and body mass index (*BMI*) for 356 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma. The mean operative time was 295±4 min (range, 120–510 min). The mean operative time for patients with BMI≥30 kg/m^2 was 299 min.

Table 2 Comparison of Preoperative Factors Associated with or without Postoperative Complications

	Any complication			Pancreatic fistula			Wound infection		
	Yes, N=135	No, *N*=221	*p* value	Yes, *N*=54	No, *N*=302	*p* value	Yes, *N*=49	No, *N*=307	*p* value
Pancreatic duct diameter (mm)	4.4±0.2	4.7±0.2	0.33	4.1±0.3	4.7±0.2	0.11	4.6±0.3	4.6±0.2	0.95
Patient age (years)	69.7±0.8	69.1±0.7	0.58	67.5±1.4	69.7±0.6	0.15	70.8±1.4	69.1±0.6	0.27
Patient weight (kg)	74.3±1.4	72.0±1.2	0.2	76.1±2.7	72.3±1.0	0.14	77.3±2.0	72.1±1.0	0.05
Patient BMI (kg/m^2)	26.9±0.4	25.9±0.3	0.07	27.3±0.7	26.1±0.3	0.11	27.7±0.7	26.0±0.3	0.03
Visceral fat thickness (cm)	2.1±0.1	1.6±0.1	<0.01	2.1±0.1	1.7±0.1	0.02	2.1±0.2	1.8±0.1	0.07
Abdominal wall fat thickness (cm)	1.8±0.9	2.1±0.8	0.07	2.0±0.2	2.0±0.1	0.87	1.9±0.2	2.0±0.1	0.74
Hip girdle fat thickness (cm)	4.2±0.2	4.4±0.2	0.24	4.0±0.3	4.4±0.1	0.25	4.3±0.3	4.3±0.1	0.96

Values expressed as mean±SEM. *p* values calculated by independent-sample *t* test

complication. The average depth of VF on preoperative CT or MRI for all patients was 1.8 cm (range, 0.2–6.9 cm). VF thickness was significantly greater for patients with any complication and those with a postoperative pancreatic fistula (Table 2).

Preoperative Predictors of Postoperative Complications

The comorbid conditions of diabetes mellitus, cardiac disease, active tobacco use, or past alcohol abuse were not found to be associated with postoperative complications. Compared to women, men were more likely to develop a complication or a pancreatic fistula after pancreaticoduodenectomy; however, gender differences among patients with or without postoperative complications did not reach statistical significance (Table 3).

The diameter of the PD on preoperative cross-sectional imaging did not correlate with any postoperative complication, including pancreatic fistula. Although the subjective preoperative assessment of pancreatic atrophy was associated with fewer overall complications, the presence of radiographic pancreatic atrophy was not associated with significantly decreased risk for developing a pancreatic fistula after pancreaticoduodenectomy. There was greater than 90% concordance between reviewers assessing radiographic pancreatic atrophy. Unfortunately, gross pancreatic gland texture at the time of operation was not recorded consistently to make any meaningful correlations with respective assessments of radiographic gland atrophy.

On multivariate analysis, patients with BMI≥30 kg/m^2 and especially those with BMI≥35 kg/m^2 were at significantly higher risk to develop a postoperative wound infection but not any other complication (Fig. 3, Table 4). VF thickness was a predictor of postoperative complications and pancreatic fistula. Fifty-one percent of 123 patients with VF thickness greater than or equal to 2.0 cm and 60% of 74 patients with VF thickness greater than or equal to 2.5 cm developed complications after pancreaticoduodenectomy. A pancreatic fistula developed in 10% of patients with a VF thickness less than or equal to 2.0 cm compared to 24 and 27% of patients with VF thickness greater than or equal to 2.0 and 2.5 cm, respectively.

Discussion

In this review, despite a 30-day mortality rate below 2%, pancreaticoduodenectomy led to postoperative complications in 38% of 356 patients who underwent resection for pancreatic adenocarcinoma. Postoperative complications were associated with significantly higher 30- and 90-day mortality rates as well as increased length of stay. The purpose of this study was to determine the risk associated with preoperative factors for developing a postoperative complication after pancreaticoduodenectomy.

The implementation of a prospectively collected postoperative complication database for pancreaticoduodenectomy has been reported previously from our institution and has demonstrated the completeness and accuracy of recording specific postoperative complications according to standardized definitions.[5] While 20 different complications were reported in this study, we focused on the three most common events namely, pancreatic fistula, wound infection, and DGE, which accounted for more than 90% of all complications. Combining a prospective pancreatic cancer database, containing demographic and clinical variables, with a postoperative complication database allowed us to assess the risk of several patient-related factors for common complications after pancreaticoduodenectomy.

In a recent study from Johns Hopkins Hospital that included nearly 3,000 patients who underwent pancreaticoduodenectomy over a 25-year period, a preoperative serum albumin value less than or equal to 3.5 g/dL or blood urea nitrogen level greater than or equal to 18 mg/dL was associated with postoperative complications.[18] We were not able to establish accurate documentation of preoperative

Table 3 Univariate Analysis of Preoperative Factors Associated with Postoperative Complications

	Any complication			Pancreatic fistula			Wound infection		
	Yes, *N*=135	No, *N*=221	*p* value	Yes, *N*=54	No, *N*=302	*p* value	Yes, *N*=49	No, *N*=307	*p* value
Gender			0.06			0.08			0.12
Male	74 (55%)	97 (44%)		32 (59%)	139 (46%)		29 (59%)	142 (46%)	
Female	61 (45%)	124 (56%)		22 (41%)	163 (54%)		20 (41%)	165 (54%)	
Active smoker	31 (23%)	48 (22%)	0.56	15 (28%)	64 (21%)	0.22	13 (27%)	66 (22%)	0.47
History of alcohol abuse	26 (19%)	44 (20%)	0.81	11 (20%)	59 (20%)	0.52	10 (20%)	60 (20%)	0.55
Diabetes mellitus	18 (13%)	44 (20%)	0.51	8 (15%)	54 (18%)	0.39	6 (12%)	56 (18%)	0.46
Coronary artery disease	15 (11%)	19 (9%)	0.52	8 (15%)	26 (9%)	0.55	2 (4%)	32 (11%)	0.86
Radiographic pancreatic atrophy	57 (42%)	113 (51%)	0.04	22 (40%)	148 (49%)	0.18	24 (49%)	146 (47%)	0.87
BMI (kg/m^2)									
≥25	83 (62%)	120 (55%)	0.19	36 (18%)	167 (56%)	0.14	33 (67%)	170 (56%)	0.13
≥30	32 (24%)	44 (20%)	0.41	13 (24%)	63 (21%)	0.62	16 (33%)	60 (20%)	0.04
Pancreatic duct diameter (mm)									
≥5	33 (25%)	64 (30%)	0.36	11 (21%)	86 (29%)	0.23	13 (26%)	84 (28%)	0.81
Visceral fat thickness (cm)									
≥2.0	63 (47%)	60 (27%)	<0.01	30 (56%)	93 (31%)	<0.01	20 (41%)	103 (34%)	0.31
≥2.5	44 (33%)	30 (14%)	<0.01	20 (37%)	54 (18%)	<0.01	16 (33%)	58 (19%)	0.03
Abdominal wall fat thickness (cm)									
≥2.0	35 (26%)	57 (26%)	0.86	14 (26%)	78 (26%)	0.99	13 (27%)	79 (26%)	0.83
Hip girdle fat thickness (cm)									
≥4.0	36 (27%)	71 (32%)	0.12	13 (24%)	94 (31%)	0.21	15 (31%)	30%)	0.77

Values expressed as number (percentage) of patients with risk factors. *p* values calculated by Fisher's exact test

weight loss compared to baseline body mass before surgical resection. Therefore, we did not feel that we could examine accurately any relationship between degrees of malnutrition, based on preoperative serum albumin alone, and complications after pancreaticoduodenectomy.

Generalized obesity, defined as BMI≥30 kg/m^2, was an independent predictor for wound infection after pancreaticoduodenectomy but not for any other complication. Furthermore, increased risk for wound infection appears to be associated somewhat linearly with a higher BMI (i.e., BMI≥35 kg/m^2). In a recent study by Lermite et al.[21], an association between BMI and postoperative wound infection was not studied; however, similar to our findings, there was no correlation between BMI≥30 kg/m^2 and the risk of pancreatic fistula or DGE after pancreaticoduodenectomy and reconstruction with pancreaticogastrostomy. It is interesting to note that the only patient-related preoperative risk factor associated with pancreatic fistula in the Lermite et al. study was coronary artery disease, a finding that was appreciated previously from a large retrospective review of 1,891 patients at Johns Hopkins Hospital.[13,21] We did not observe an association between coronary artery disease and pancreatic fistula in our study.

Generalized obesity and heart disease have long been recognized as significant risk factors for minor and major complications after pancreaticoduodenectomy.[16] In the past, anthropometric studies of obesity and body fat distribution have characterized obese human body forms into three types: gynoid, android, and intermediate.[22] Gynoid obesity (i.e., pear-shaped) is characterized by lower body fat predominance, whereas android obesity (i.e., apple-shaped) is characterized by upper body fat centralization. The association between obesity type and concomitant morbidity such as diabetes mellitus, hypertension, and gynecologic abnormalities has been studied in the past, but no studies have attempted to correlate body fat distribution with specific postoperative complications.[22–24]

In this study, we performed a retrospective comparison between preoperative radiographic body fat distribution and complications after pancreaticoduodenectomy. The thickness of AW and HG fat did not correlate with overall or specific postoperative complications; however, the depth of retrorenal fat was a significant risk factor for complications after pancreaticoduodenectomy namely, pancreatic fistula and wound infection. The preferred cutoff value for VF as a risk factor for postoperative complications was 2.0 cm; however, there were no statistical differences in AW or HG thickness for patients with VF<2.0 cm vs those with VF≥ 2.0 cm. Retrorenal fat thickness can be measured precisely at the level of the left renal vein; however, it has several limitations as a pure surrogate index marker for the degree of VF mass. Reproducible retrorenal fat measurements are

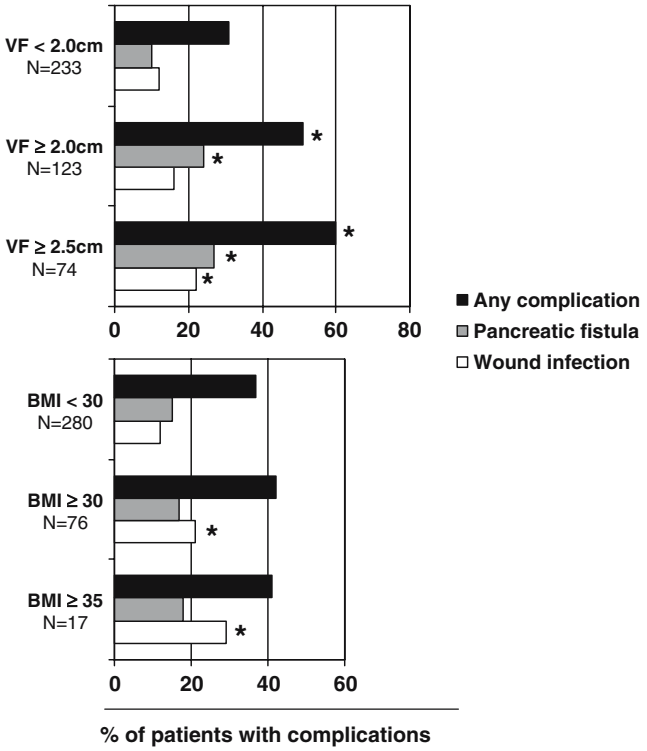

Figure 3 The percentage of patients who developed postoperative complications (any complication, pancreatic fistula, wound infection) on the basis of visceral fat (*VF*) thickness and body mass index (*BMI*, kg/m^2). *Asterisks* designate significant differences in the incidence of each complication according to the categorized risk factor, VF and BMI, on multivariate analysis.

affected by body positioning during cross-sectional imaging, and although not significantly different, VF content tends to be higher for men (median male VF=2.2 cm; median female VF=1.6 cm). The mean BMI and VF thickness for women was 25.8 kg/m^2 and 1.8 cm, respectively, vs 26.8 kg/m^2 and 2.2 cm for men; p=0.06. Even after adjusting for gender, VF thickness appears to be an independent risk factor for postoperative complications. We did not characterize Whipple specimens for the presence of pancreatic steatosis histopathologically; thus, we were not able to correlate VF thickness with pancreatic fat content. It was not possible to assess the subjective difficulty of performing the pancreatic anastomosis in patients with large amounts of VF; however, similar to BMI (Fig. 2), we did not observe a linear relationship between VF thickness and operative time. It is possible that retroperitoneal peripancreatic fat complicates the technical aspects of pancreaticojejunostomy by obscuring the placement of secure pancreatic parenchymal sutures. The majority of the pancreaticojejunostomies in this study were performed with a through-and-through pancreatic transfixation suturing technique that reduces the likelihood of insecure purchases of the pancreatic parenchyma during anastomosis.

We were not able to correlate postoperative complications with the appearance of the pancreas (i.e., normal or atrophic) or the diameter of the PD on preoperative cross-sectional imaging. Because of limited detailed operative data, we were not able to compare our subjective radiologic assessment of the pancreas with gross gland texture at the time of operation. Thus, we could not assess whether a

Table 4 Multivariate analysis of preoperative factors associated with postoperative complications

	Any complication			Pancreatic fistula			Wound infection		
	Percent	HR	p value	Percent	HR	p value	Percent	HR	p value
Gender									
Female (N=185)	33			12			11		
Male (N=171)	43	1.28	0.09	19	1.16	0.2	17	1.25	0.32
BMI (kg/m^2)									
<25 (N=150)	34			12			11		
<30 (N=280)	37	1.01	0.76	15	0.98	0.97	12	1.05	0.1
30 (N=76)	42	1.04	0.07	17	1.05	0.11	21	1.10	0.03
35 (N=17)	41	1.04	0.09	18	1.55	0.65	29	2.54	0.01
Visceral fat thickness (cm)									
<2.0 (N=233)	31			10			12		
≥2.0 (N=123)	51	1.59	<0.01	24	1.36	0.02	16	1.29	0.07
≥2.5 (N=74)	60	2.98	<0.01	27	2.35	0.02	22	1.60	0.02
Radiographic pancreatic atrophy									
Yes (N=186)	34			13			14		
No (N=170)	47	1.60	0.04	18	1.52	0.18	14	0.95	0.87

Values expressed as percentage of patients with complications; p values calculated by a logistic regression model
HR Hazard ratio

radiographically appearing atrophic pancreas correlates with firm gland texture, a finding that has been shown to be protective against pancreatic fistula.[11,13] We did not attempt to correlate radiologic pancreatic appearance with histologic pancreatic steatosis, periductal fibrosis, acinar necrosis, or inflammatory parenchymal infiltration. Future prospective studies should be directed at better characterizing pancreatic texture and consistency in obese patients with large amounts of VF to determine the gland features that potentiate pancreatic fistula after pancreatic resection.

Retrospective studies have reported that a large PD diameter, which is appreciated intraoperatively (i.e., main duct >3 mm), may be a protective factor against postoperative pancreatic leak.[14,25,26] However, we were not able to demonstrate a relationship between pancreatic fistula and duct diameter that is measured on preoperative scans. All patients in this study underwent resection for pancreatic adenocarcinoma, and 70% of patients had a main PD diameter greater than or equal to 3 mm on preoperative imaging. Therefore, it is inherently difficult to assess the influence of radiographic gland atrophy and PD size on developing a postoperative pancreatic fistula.

The aim of this study was to identify preoperative patient-related factors and radiologic findings that predispose to postoperative complications after pancreaticoduodenectomy for pancreatic cancer. The subjective difficulty of pancreaticoduodenectomy in obese patients leading to potential postoperative complications was not apparent in this study. Generalized obesity, estimated by BMI, was only associated with a higher risk of wound infection. Body fat distribution, more specifically the degree of visceral adiposity estimated by the thickness of retrorenal fat, was found to be a risk factor for postoperative complications after pancreaticoduodenectomy and appears to be independent of the potential contributions from gender, generalized obesity, or obesity type based on AW and HG fat distribution (i.e., gynoid vs android habitus). Patients with retrorenal fat thickness greater than or equal to 2.5 cm are nearly three times more likely to develop complications after pancreaticoduodenectomy.

Perioperative management of patients undergoing pancreaticoduodenectomy for cancer should account for preoperative radiologic findings related to VF mass. In this study, patients with retrorenal fat thickness greater than or equal to 2.5 cm are nearly 2.5 times more likely to develop a pancreatic fistula after pancreaticoduodenectomy. Appropriate risk adjustments should be considered for patients with benign pancreatic disease who are being evaluated for pancreaticoduodenectomy. Adjunctive operative techniques and therapies (e.g., somatostatin analogues) aimed at reducing the chances of a pancreatic leak after pancreaticoduodenectomy should be considered in an obese patient with a large amount of retroperitoneal fat.

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Restorative Proctocolectomy for Ulcerative Colitis: Impact on Lipid Metabolism and Adipose Tissue and Serum Fatty Acids

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Abstract The aim of this prospective study was to evaluate the changes of the metabolism of circulating and storage lipids in patients with ulcerative colitis after restorative proctocolectomy. Fifteen consecutive patients and 15 sex- and age-matched healthy controls were enrolled. Disease activity, diet, inflammatory parameters, plasma lipoprotein concentrations, and fatty acids (FA) of serum phospholipids and of the subcutaneous adipose tissue were assessed at colectomy and at ileostomy closure. In ulcerative colitis patients, total cholesterol and docosahexaenoic acid were lower than in healthy subjects ($p<0.01$ and $p<0.05$). The median interval between colectomy and ileostomy closure was 6 (range 2–9) months. During that interval, the inflammatory parameters improved, high-density lipoproteins (HDL) cholesterol increased ($p<0.01$), and low-density (LDL) cholesterol decreased ($p=0.01$). At ileostomy closure, serum arachidonic acid levels were increased ($p=0.04$), whereas serum oleic acid level was decreased ($p=0.02$). In this interval, no significant alteration, either in serum n-3 FA precursors or in the FA of subcutaneous adipose tissue, was observed. The increase of serum arachidonic acid after colectomy might suggest a lower utilization for inflammatory process. The reduction of LDL cholesterol is an index of malabsorption probably due to the accelerated transit and to the exclusion of the terminal ileum caused by the covering ileostomy.

Keywords Ulcerative colitis · Restorative proctocolectomy · Cholesterol · Fatty acids

Introduction

Restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) is the first choice for the elective surgical treatment of patients affected by ulcerative colitis (UC)[1,2]. Most patients suffer dietary restrictions with an important impact on their quality of life, but there are

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further nutritional and metabolic implications in the UC and RPC physiology.[3] In active UC patients, systemic inflammation and the accelerated transit through the colon lead to catabolic situation that may be clinically evident with weight loss, anemia, and low albuminemia. RPC produces the resolution of the inflammatory status at the price of the removal of the whole colon. In this new intestinal situation, the accelerated transit persists, and during the period when patients have a diverting loop ileostomy, the last 70 cm of ileum are excluded. This new intestinal configuration may directly affect lipid metabolism. In fact, fatty acids and cholesterol are absorbed mainly in the small bowel.

Fatty acids (FA) are the main components of the cell membrane, and some polyunsaturated fatty acids (PUFAs) are precursors of the eicosanoids, which are important mediators of inflammation.[4,5] Dietary FA may play an important role in the ulcerative colitis pathogenesis,[6,7] and an abnormal plasmatic PUFA pattern was described in active and non-active inflammatory bowel disease (IBD).[8,9] As these alterations do not seem to persist after colectomy, the increase in plasma n-3 PUFA in UC patients may be due to, or at least be related to, the inflammation.[10] PUFA have been also investigated for their efficiency after oral supplementation in reducing the relapse in UC.[11,12] n-3 PUFA can produce alterations in the composition of cellular membrane[13] causing the decrease of the expression of some cytokines, adhesion molecules and leukocytes chemotaxis, and the increase of the synthesis of eicosanoids derived from the eicosapentaenoic acid that can decrease the pro-inflammatory activity.[14–16] Furthermore, n-3 PUFA can change the permeability of tight junctions of intestinal epithelial cells[17] and can decrease the oxidative stress in patients with UC,[7] competing with n-6 PUFA and inhibiting the production of metabolites of arachidonic acid such as leukotriene B4 and prostaglandin E2.[18]

After RPC, lipid absorption impairment was reported by Hylander et al.[19] who described steatorrhea. Similarly, M'koma et al.[20] described serum cholesterol and alpha lipoprotein decrease and triglycerides increase during the period of the diverting ileostomy with a complete restoration of a normal plasma lipoprotein concentration 1 year after ileostomy closure. Furthermore, Hakala et al.[21] report lower serum cholesterol and triglycerides levels in RPC patients with the loss of feedback between absorption and synthesis, and they suggest ileal bacterial overgrowth in the terminal ileum as the cause of the cholesterol impaired absorption. Moreover, cholesterol metabolism after colectomy was studied in relation to gallstones formation.[22,23]

The aim of this study was to define the impact of RPC on lipid metabolism in patients affected by UC in terms of fatty acid composition in serum and in adipose tissue and in terms of serum plasma lipoprotein concentrations.

Materials and Methods

Study Design

The study was performed according to the Helsinki declaration principles. The patients' medical records were revised, and the following data were included: duration, extension, and activity of the IBD; drugs [5-amino-salicylic acid (5-ASA), steroids, or immuno-suppressors] including doses and number of cycles since disease onset; dates and findings of all colonoscopies, colonic biopsies; surgery with its indication, findings, and histology; date of the last follow-up and vital status; and presence of hyperlipidemia.

At the time of RPC and of stoma closure, on the day of admittance, after a 12 h fasting, adequate blood samples for the following analysis were obtained: FA, triglyceridemia, total cholesterolemia, HDL, LDL, apolipoprotein A2, albuminemia, full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), coagulation parameters, homocysteinemia, and creatinine. The plasma lipoprotein concentrations were related to anthropometrical and nutritional measures [body mass index (BMI) and albuminemias] and to inflammatory measure [CRP, ESR, and white blood cell count (WBC)].

At each point of the study, the diet was carefully evaluated to identify the total amount of calories and the quality of the aliments with a specific and validated food frequency questionnaire.

Each patient had a subcutaneous fat sample collected from the anterior abdominal wall at RPC and at ileostomy closure.[24,25]

Patients

All the consecutive patients who attended to our department to have RPC for UC since December 2004 to March 2006 were enrolled and prospectively followed. Adequate informed consent was obtained from all persons involved. Patients who presented hereditary lipid metabolism disorders were excluded from this study. Fifteen patients were enrolled in our study. They were ten men and five women, and their median age was 45 (29–66). The indication for RPC was severe or refractory UC in 11 cases and UC and dysplasia or cancer in 4 cases. The operations were performed by the same operator (I.A.) with stapled J pouch. In the postoperative course, a case of endocarditis and an

Table 1 Serum Lipid Distribution in UC Patients at RPC and in Healthy Sex- and Age-Matched Subjects

	UC patients at RPC		Healthy subjects		*P* level
	Median	Range	Median	Range	
Gender	10 male	5 female	10 male	5 female	
Age	45	(29–66)	45	(29–65)	0.854
Total cholesterol	164	(80–242)	197	(169–285)	0.009
Triglycerids	103	(56–161)	94	(48–236)	0.852
Cholesterol-HDL	43	(19–65)	54	(36–83)	0.014
Cholesterol-LDL	100	(26–160)	116	(98–202)	0.051
14: 0 (myristic)	0.605	(0.25–1.54)	0.55	(0.31–0.72)	0.730
16: 0 (palmitic)	30.65	(29.3–36.9)	28.93	(28.04–33.19)	0.000
16: 1 n7 (palmitoleic)	1.23	(0.49–1.86)	0.61	(0.44–1.12)	0.001
18: 0 (stearic)	11.9	(11.12–13.77)	14.125	(12.65–17.91)	0.000
18: 1 n-9 (oleic)	17.55	(10.52–20.7)	13.49	(10.7–17.89)	0.002
18: 2 n–6 (linoleic)	19.75	(16.79–26.91)	22.655	(16.51–24.86)	0.031
18:3 n-3 (α-linolenic)	0.18	(0.13–0.22)	0.19	(0.11–0.27)	0.594
20: 1 n9 (eicosanoic)	0.19	(0.14–0.22)	0.18	(0.1–0.19)	0.111
20: 3 n-6 (dihomoγlinolenic)	2.81	(2–4.86)	3.85	(3.29–4.97)	0.108
20: 4 n-6 (arachidonic)	8.90	(6.19–11.32)	9.96	(7.73–13.67)	0.098
20:5 n-3 (eicosapentaenoic)	0.54	(0.23–1.29)	0.555	(0.44–1.59)	0.215
22: 4 n-6 (adrenic)	0.41	(0.23–0.64)	0.41	(0.27–0.49)	0.891
22: 5 n-3 (docosopentaenoic)	0.74	(0.43–2.94)	0.735	(0.52–1.05)	0.890
24: 0 (lignoceric)	0.1	(0.07–0.26)	0.105	(0.07–0.16)	0.766
22: 6 n-3 (docosahexaenoic)	3.09	(1.73–4.57)	3.545	(2.14–5.68)	0.042
24: 1 (nervonic)	0.12	(0.09–0.18)	0.14	(0.08–0.25)	0.884
Saturated FA	43.83	(0.00–49.53)	44.00	(41.70–49.45)	0.844
Monounsaturated FA	19.12	(0.00–22.70)	14.05	(11.62–19.00)	0.005
Polyunsaturated-6 FA	31.74	(0.00–40.77)	35.91	(30.58–40.89)	0.003
Polyunsaturated-3 FA	4.27	(0.00–6.92)	4.75	(8.12–3.49)	0.021

anastomotic leak occurred. The median interval between RPC and ileostomy closure was 6 (2–9) months. Ileostomy closure was more delayed in those patients who had the above-mentioned complications.

A sex- and age-matched group of 15 healthy subjects was enrolled as control. They were ten men and five women, and their median age was 45 (29–65).

Dietary Evaluation

This questionnaire was designed to estimate daily intake of foods and nutrients during the previous 2 weeks and information on dietary habits. It consists of a food list divided for meal (breakfast, lunch, dinner, and two breaks) that reflects the habitual Italian diet[26] and additional question for milk. The Food Frequency Questionnaire (FFQ) was administered by an expert dietician. Patients selected foods depending on diet habits, standard portion size was assigned to each questionnaire item with the help of an atlas,[27] and respondents were requested to assess the frequency of each one. The data collected was analyzed in agreement to Greenfield and Southgate recommendations.[28]

Inflammation Status

The inflammatory activity was assessed by quantifying ESR, WBC, platelets blood count (PLT), and CRP. ESR was measured by the Westergren method. CRP was detected by immuno-nephelometry. Total proteinemia and albuminemia were assessed with the biuret method. WBC and hemoglobinemia were obtained with standard full blood cell count.

Biochemical Assays

Fasting plasma glucose was measured by the glucose-oxidase method and HbA1c by high-performance liquid chromatography (Bio-Rad Laboratories, Milan, Italy). Cholesterol and triglycerides in the plasma were measured by enzymatic methods.[29,30] HDL cholesterol was measured after precipitation of apo-B containing lipoproteins with polyanions.[31] LDL cholesterol was calculated according to the Friedewald equation except when triglycerides were >4.52 mmol/l.[32]

Plasma phospholipid fatty acid composition was determined after lipid extraction by the method of Folch et al.[33] Phospholipids were isolated by application of the lipid

Table 2 Serum Lipid Distribution in UC Patients at Ileostomy Closure and in Healthy Sex- and Age-Matched Subjects

	UC patients at ileostomy closure		Healthy subjects		*p* level
Total cholesterol	141	(86–203)	197	(169–285)	0.000
Triglycerids	104	(47–215)	94	(48–236)	0.756
Cholesterol-HDL	56	(25–84)	54	(36–83)	0.934
Cholesterol-LDL	52	(24–139)	116	(98–202)	0.000
14: 0	0.43	(0.27–1.09)	0.55	(0.31–0.72)	0.259
16: 0	32.65	(29.81–35.86)	28.93	(28.04–33.19)	0.000
16: 1 n7	1.03	(0.65–1.68)	0.61	(0.44–1.12)	0.000
18: 0	11.71	(9.17–14.27)	14.125	(12.65–17.91)	0.000
18: 1 n9	15.36	(10.66–19.54)	13.49	(10.7–17.89)	0.251
18: 2 n6	19.72	(14.67–24.74)	22.655	(16.51–24.86)	0.054
18: 3 n3	0.17	(0.08–0.32)	0.19	(0.11–0.27)	0.491
20: 1 n9	0.14	(0.05–0.25)	0.18	(0.1–0.19)	0.287
20: 3 n6	3.47	(2.47–5.43)	3.85	(3.29–4.97)	0.370
20: 4 n6	9.79	(8.38–13.9)	9.96	(7.73–13.67)	0.696
20: 5 n3	0.53	(0.42–1.21)	0.555	(0.44–1.59)	0.448
22: 4 n6	0.43	(0.29–0.61)	0.41	(0.27–0.49)	0.290
22: 5 n3	0.75	(0.63–0.95)	0.735	(0.52–1.05)	0.420
24: 0	0.08	(0.06–0.14)	0.105	(0.07–0.16)	0.150
22: 6 n3	2.66	(1.28–4.52)	3.545	(2.14–5.68)	0.009
24: 1	0.18	(0.08–0.39)	0.14	(0.08–0.259)	0.395
Saturated FA	46.12	(41.75–47.92)	44.00	(41.70–49.45)	0.077
Monounsaturated FA	16.00	(0.00–21.35)	14.05	(11.62–19.00)	0.310
Polyunsaturated-6 FA	34.61	(0.00–39.29)	35.91	(30.58–40.89)	0.102
Polyunsaturated-3 FA	3.91	(0.00–6.88)	4.75	(8.12–3.49)	0.037

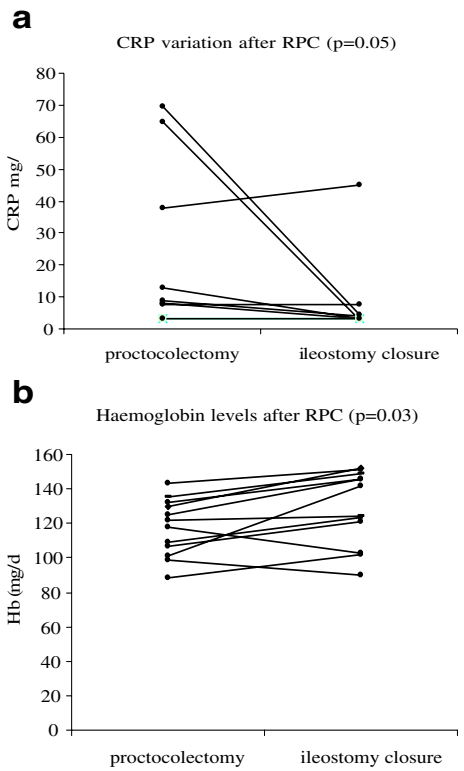

Figure 1 **a**, **b** Inflammatory parameters significantly improved after RPC.

extract to a column of silica coupled with aminopropyl groups (Bond Elute NH2, Analytichem International, Harbor City, CA, USA). After transmethylation by the method of Morrison and Smith,[34] fatty acids were determined by gas chromatograph Perkin Elmer AutoSystem XL, with a capillary column Omegavax 320 (30 m × 0.32 mm ID, 0.25 μm film). Column conditions were 200°C, injection port 250°C, and flame ionization detector 260°C. Helium was used as carrier gas (linear velocity, 0.25 m/s); the split ratio was 100:1. Fatty acid peaks were identified by comparison with standard mixtures of fatty acids supplied by Supelco, Bellefonte, PA, USA. The amounts of individual fatty acids were calculated as relative absorption percentage in the chromatographic result, with the evaluated fatty acids as 100%. Only fatty acid percentages more than 0.2% are shown in "Results".

Samples of adipose tissue, weighing about 10–50 mg, were stocked at −80°C until the analysis and then washed and centrifuged three times (2,500 rpm for 2 min) in 12 ml of NaCl 0.95 solution to remove erythrocytes. Adipose tissue samples in 1 ml of saline solution were extracted with chloroform /methanol (2:1) according to the technique of Folch.[30] The lipid fraction was trans-methyled with boric trifluoride in methanol at 100°C for 10 min to obtain methylic esthers of each fatty acid. These acids were isolated

Table 3 Disease Activity and Metabolic Parameters in UC Patients at RPC and Ileostomy Closure

	RPC		Ileostomy closure		*p* level
	Median	Range	Median	Range	
Stool per day	5.00	2.00–20.00	3.50	1.00–10.00	1.000
WBC /ml	8.41	4.30–11.74	7.63	3.86–10.96	0.239
Hb (g/l)	118.00	88.00–159.00	133.00	90.00–152.00	0.034
CRP (mg/l)	8.12	3.13–242.00	3.16	2.98–45.00	0.050
ESR (mm/h)	27.00	10.00–81.00	24.50	6.00–58.00	0.281
Fasting glucose (mmol/L)	4.07	1.60–7.30	4.90	3.30–5.90	0.028
Total protein (g/L)	72.00	54.00–86.00	77.00	73.00–88.00	0.013
Omocystein	13.70	7.27–99.20	11.46	8.00–97.60	0.295
Apolipoprotein A	1.45	0.71–2.06	1.78	1.34–1.98	0.116
Apolipoprotein B	0.85	0.43–1.28	0.56	0.40–1.10	0.017
Apo B/Apo A	0.52	0.24–1.35	0.34	0.25–0.74	0.017
Lp(A)	112.00	25.00–813.00	239.00	25.00–1,260.00	0.144

with a gas chromatograph Perkin Elmer Auto System XL, with a capillary column Omegavax 320 (30 m×0.32 mm, ID 0.25 μm film).

Statistical Analysis

Data were presented as median (range) where appropriate. Set the standardized effect size (expected difference of cholesterol and FA concentration in the different stages divided by the expected standard deviation) at 1.00, a level of statistical significance (α) at 0.05, and a power ($1-\beta$) at 0.20; the consequent sample size required for comparison was 12 patients.

Non-parametric Wilcoxon matched-pair two-tailed test was used to compare continuous variables. Mann–Whitney *U* test was used to compare continuous variables between UC patients and healthy controls. Fisher exact test was used for frequency analysis. Linear association between continuous variables such as serum cholesterol and FA concentration and inflammatory parameters was quantified using Spearman's rank correlation test. Statistical significance was set at $p<0.05$.

Results

In UC patients at RPC and at ileostomy closure, total cholesterol ($p<0.01$) and LDL cholesterol ($p=0.05$) were significantly lower than in healthy subjects. In the serum of UC patients at RPC and ileostomy closure, palmitic acid (16:0) was significantly more represented than in healthy subjects ($p<0.01$), whereas stearic (18:0) acids percentage were lower in UC patients at RPC and ileostomy closure compared to healthy controls ($p<0.01$). Palmitoleic (16:1 n7) and oleic acid (18:1n 9) were more represented in patients with UC at RPC than in healthy subjects ($p<0.01$), whereas only palmitoleic acid was more represented in UC patients at ileostomy closure than healthy subjects

Table 4 Dietary Intake, Weight, and BMI at RPC and at Ileostomy Closure

	RPC		Ileostomy closure		*p* level
	Median	Range	Median	Range	
Weight (kg)	67.50	50.00–95.00	68.50	50.00–101.00	0.575
BMI (kg/m^2)	23.06	19.53–31.74	21.88	19.92–29.40	0.327
Diet caloric intake (cal/day)	1,875.00	101.00–3,320.00	1,959.00	1,430.00–2,998.00	0.753
Diet proteic intake (g/day)	75.80	57.00–113.16	81.73	58.41–110.26	0.345
Diet glucose intake	250.00	145.00–482.00	239.00	200.00–452.00	0.753
Diet lipid intake	57.00	38.00–116.00	59.00	43.72–77.81	0.753
-Diet saturated FA intake	18.38	11.96–34.08	19.86	15.04–39.91	0.249
-Diet monounsaturated FA intake	31.16	7.78–48.60	25.17	15.90–37.32	0.600
-Diet polyunsaturated FA intake	4.96	1.08–13.54	6.71	3.86–8.69	0.834

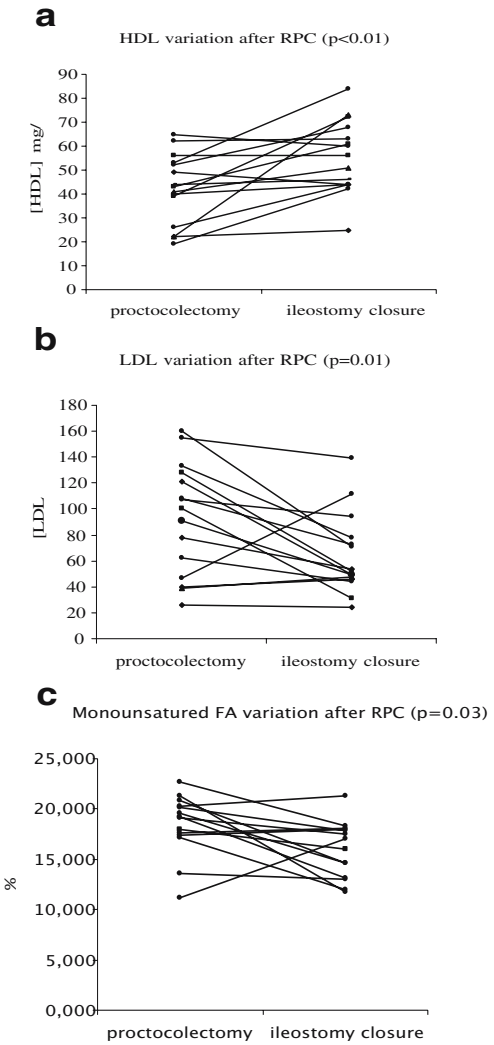

Figure 2 **a**, **b** HDL and LDL significantly improved after RPC. **c** Serum monounsaturated FA significantly decreased after RPC.

($p<0.01$). The monounsaturated fatty acids family was more represented in UC patients at RPC than in healthy patients ($p<0.01$). Docosohexaenoic (22:6 n3) and n-3 PUFAs family were lower in UC patients at RPC and ileostomy closure compared to healthy controls ($p<0.05$). The linoleic acid (18:2 n6) and the n-6 PUFAs were significantly lower at RPC compared to healthy controls ($p<0.01$). The comparisons of FA, plasma lipoprotein concentrations between UC patients, and healthy subjects are shown in Tables 1 and 2.

As shown in Fig. 1a, b, during the interval between RPC and ileostomy closure, the systemic inflammation improved in terms of CRP that reached a median value in the range of normality and the level of hemoglobin ($p<0.05$). The patient who maintained an elevated CRP level was the one who had an anastomotic leakage. In the interval between RPC and ileostomy closure, patients significantly increased their fasting glycemia and their total serum proteins ($p<0.05$). Inflammatory and metabolic parameters at RPC and at ileostomy closure were shown in Table 3.

During the same interval, there were no significant modifications in the dietary intake neither in terms of total calories nor of percentage of single component of the diet. Weight and diet variations between RPC and ileostomy closure are shown in Table 4.

Several correlations between the food frequency questionnaire and the plasma phospholipid fatty acid percentages were evident: inverse correlation between the saturated fatty acid in the diet and the α-linolenic acid ($r=-0.743$, $p=0.022$), monounsaturated fatty acid of the diet and LDL cholesterol ($r=0.889$, $p=0.002$), and palmitic acid ($r=-0.904$, $p=0.001$) and eicosanoic acid ($r=0.783$, $p=0.022$).

In spite of a similar total serum cholesterol, UC patients between RPC and ileostomy closure showed significant modification of the lipoproteins [median HDL cholesterol: from 43 (19–65) to 56 (25–84) mg/dl, $p<0.01$; median LDL-cholesterol: from 101 (26–160) to 52 (24–139) mg/dl, $p=0.01$]. At ileostomy closure, serum oleic acid and the monounsaturated family decreased compared to levels at RPC ($p=0.04$; $p=0.03$), whereas serum arachidonic acid significantly increased after RPC. No significant alteration in serum n-3, n-6, and saturated fatty acid families was observed in UC patients in the interval between RPC and ileostomy closure. The variations of the lipid and phospholipids fatty acid profile are shown in Table 5 and Fig. 2a–c.

No significant variations in the composition of FA of subcutaneous adipose tissue were observed between RPC and ileostomy closure. The comparisons of FA profile in the subcutaneous tissue between UC patients at RPC and, after 6 months, at ileostomy closure are shown in Table 6.

Discussion

RPC is the first choice for the elective surgical treatment of patients affected by UC.[1,2] Either UC on itself or RPC may cause dietary restrictions and have nutritional and metabolic implications.[3] Active UC implies systemic inflammation and accelerated transit through the colon and therefore through the whole intestinal tract. RPC leads to the resolution of inflammation but the accelerated transit persists and, whereas patients have a diverting loop ileostomy, the last 70 cm of ileum are excluded. As described by several authors in both these situations, lipid metabolism may be affected.[8,9,10,19,20,35] The aim of this study was to define the impact of RPC on lipid metabolism in patients affected by UC in terms of plasma and adipose tissue phospholipid fatty acid composition and in terms of plasma lipoprotein concentrations.

Table 5 Serum Lipid Distribution in UC Patients at RPC and at Ileostomy Closure

	RPC			Ileostomy closure			*p* level
	Patients	Median	Range	Patients	Median	Range	
Total cholesterol	15	164.00	(80.00–242.00)	15	141.00	(86.00–203.00)	0.191
Triglycerids		103.00	(56.00–161.00)		104.00	(47.00–215.00)	0.460
Cholesterol-HDL		43.00	(19.00–65.00)		56.00	(25.00–84.00)	0.009
Cholesterol-LDL		101.00	(26.00–160.00)		52.00	(24.00–139.00)	0.012
14: 0	14	0.61	(0.25–1.54)	14	0.43	(0.27–1.09)	0.221
16: 0		30.66	(29.30–36.90)		32.65	(29.81–35.86)	0.198
16: 1 n-7		1.23	(0.49–1.86)		1.03	(0.65–1.68)	0.124
18: 0		11.90	(11.12–13.77)		11.71	(9.17–14.27)	0.414
18: 1 n-9		17.55	(10.52–20.70)		15.37	(10.66–19.54)	0.026
18: 2 n-6		19.76	(16.79–26.91)		19.73	(14.67–24.74)	0.875
18: 3 n-3		0.14	(0.00–0.22)		0.13	(0.00–0.23)	0.638
20: 1 n-9		0.18	(0.00–0.22)		0.11	(0.00–0.25)	0.108
20: 3 n-6		2.81	(2.00–4.86)		3.48	(2.47–5.43)	0.177
20: 4 n-6		8.91	(6.19–11.32)		9.80	(8.38–13.90)	0.041
20: 5 n-3		0.54	(0.23–1.29)		0.53	(0.42–1.21)	0.209
22: 4 n-6		0.38	(0.00–0.64)		0.44	(0.29–0.61)	0.300
22: 5 n-3		0.74	(0.43–2.94)		0.75	(0.63–0.95)	0.402
24: 0		0.09	(0.00–0.26)		0.03	(0.00–0.14)	0.139
22: 6 n-3		3.06	(0.00–4.57)		2.66	(1.28–4.52)	0.331
24: 1		0.10	(0.0–0.180)		0.15	(0.00–0.39)	0.013
Saturated FA		43.83	(0.00–49.53)		46.12	(41.75–47.92)	0.397
Monounsaturated FA		19.12	(0.00–22.70)		16.00	(0.00–21.35)	0.035
Polyunsaturated-6 FA		31.74	(0.00–40.77)		34.61	(0.00–39.29)	0.158
Polyunsaturated-3 FA		4.27	(0.00–6.92)		3.91	(0.00–6.88)	0.470
Δ 9/16 desaturase		0.04	(0.01–0.06)		0.03	(0.02–0.05)	0.048
Δ 9/18 desaturase		1.44	(0.81–1.85)		1.19	(0.78–1.93)	0.124
Δ 5 desaturase		2.77	(4.10–2.02)		2.97	(1.62–4.49)	0.683

As expected, colectomy permitted the complete resolution of the systemic inflammation as shown by CRP, total serum proteins, and hemoglobin that reached values in the range of normality in the interval between RPC and ileostomy closure. Although the source of inflammation and of inflammatory mediators was removed, the new equilibrium is far to be completely restored.

It has been demonstrated that the measurement of plasma phospholipid fatty acids is an objective indicator of usual dietary fatty acid composition.[36] In fact, we found correlations between dietary fatty acid intake at the food frequency questionnaire and plasma fatty acid composition. The dietary intake did not substantially modify in part because it is difficult to change alimentary habits that have lasted for years but mainly because of the presence of the ileostomy, which forces patients to have a quite strict diet to minimize nutrients and water loss. Consequently, the BMI of the patients did not improve. Only the monounsaturated fatty acid family and the oleic acid, which represented mainly the alimentary olive oil intake, significantly decreased after RPC. The dietary intake of monounsaturated fatty acids, although not significantly, also decreased. The unvaried composition of FA of subcutaneous adipose tissue might be due to the relative short time between the RCP and ileostomy and the substantially unchanged diet.

During the interval between RPC and ileostomy closure, we observed a significant increase of HDL cholesterol, whereas total cholesterol and LDL cholesterol decreased significantly and were lower in UC patients at RPC and at ileostomy closure than in healthy subjects. These results seemed to be consistent with what reported by Hylander et al.[19] and M'koma et al.[20] During the period of the diverting ileostomy, the terminal ileum is excluded with the partial loss of the entero-hepatic cholesterol feedback causing an impairment of cholesterol absorption. The complete restoration of a normal plasma lipoprotein concentrations is reported to be reached approximately 1 year after ileostomy closure[20] even if Hakala et al.[21] seem to suggest that ileal bacterial overgrowth in the terminal ileum can continue to cause impaired cholesterol absorption after ileostomy closure.

n-3 PUFA can change the permeability of tight junction of intestinal epithelial cells[17] and can decrease the oxidative stress in patients with UC,[7] competing with n-6 PUFA and

Table 6 Subcutaneous Lipid Distribution in UC Patients at RPC and at Ileostomy Closure

	RPC			Ileostomy closure			
	Patients	Median	Range	Patients	Median	Range	*p* level
14: 0	10	3.18	(1.93–4.17)	10	3.42	(2.51–3.93)	0.575
16: 0		23.98	(18.86–26.89)		24.22	(23.30–31.69)	0.169
16: 1 n-7		4.44	(2.50–6.57)		4.12	(3.35–6.85)	0.959
18: 0		4.47	(3.48–6.29)		4.89	(3.27–5.61)	0.721
18: 1 n-9		49.45	(45.20–54.23)		47.86	(43.93–51.92)	0.241
18: 2 n-6		12.12	(8.80–21.39)		11.42	(8.83–18.53)	0.285
18: 3 n-3		0.31	(0.22–0.61)		0.32	(0.28–0.64)	0.086
20: 1 n-9		0.57	(0.48–0.98)		0.57	(0.37–0.86)	0.139
20: 3 n-6		0.19	(0.14–0.28)		0.21	(0.14–0.29)	0.359
20: 4 n-6		0.33	(0.28–0.50)		0.35	(0.27–0.48)	0.959
20: 5 n-3		0.04	(0.02–0.12)		0.04	(0.00–0.08)	0.401
22: 4 n-6		0.12	(0.07–0.28)		0.12	(0.00–0.25)	0.906
22: 5 n-3		0.14	(0.05–0.22)		0.14	(0.06–0.21)	0.834
24: 0		0.02	(0.00–0.07)		0.00	(0.00–0.03)	0.281
22: 6 n-3		0.12	(0.00–0.30)		0.10	(0.00–0.22)	0.683
24: 1		0.00	(0.00–0.05)		0.01	(0.00–0.03)	0.273
Saturated FA		31.65	(24.70–35.41)		32.31	(29.91–39.91)	0.093
Monounsaturated FA		53.86	(51.63–59.19)		52.95	(49.64–59.40)	0.093
Polyunsaturated-6 FA		12.78	(9.84–22.28)		12.10	(9.42–19.26)	0.386
Polyunsaturated-3 FA		0.62	(0.35–1.24)		0.61	(0.44–1.00)	0.646
Δ 9/16 desaturase		0.19	(0.10–0.27)		0.16	(0.14–0.29)	0.575
Δ 9/18 desaturase		10.80	(7.98–14.84)		9.80	(8.18–15.84)	0.386
Δ 5 desaturase		1.87	(1.47–2.14)		1.78	(1.15–2.57)	0.721

inhibiting the production of metabolites of arachidonic acids, such as leukotrien B4 and prostaglandin E2.[18] In active and remission UC patients, PUFA were described to have an abnormal pattern: increase in n-3 and decrease in n-6. According to Esteve-Comas et al.,[10] these alterations seem to normalize after colectomy, and therefore, these authors considered them as a mere epiphenomenon of the inflammatory status. On the contrary, in our series, whereas linoleic acid (18:2 n-6) was significantly lower at RPC compared to healthy controls but normalized at ileostomy closure, docosohexaenoic (22:6 n3) remained significantly lower both at RPC and at ileostomy closure. The same phenomenon was observed when considering the whole families: n-6 PUFAs and n-3 PUFAs families were significantly lower at RPC in UC patients compared to healthy controls, but at ileostomy, only the n-3 PUFAs family remained significantly low. The n-3 PUFA deficiency is not corrected by the removal of the inflamed colon, so it might be due to malabsorption as a consequence of the accelerated transit or, alternatively, of an intrinsic failure of the n-3 synthetic pathway. This deficiency might be involved in the maintenance of colonic inflammation in patients with UC.

In our series, similarly to what reported by Esteve-Comas,[10] either at RPC or at ileostomy closure, palmitic (16:0) was significantly more represented than in healthy subjects. On the contrary, stearic (18:0) acids levels were lower in UC patients at RPC and ileostomy closure compared to healthy controls, whereas Esteve et al.[10] reported it to be increased compared to healthy controls. Palmitoleic (16:1 n7) and oleic acid (18:1n9) were more represented in patients with UC at RPC than in healthy subjects and, similarly to what observed in Crohn's disease patients by Geerling et al.,[37] the whole monounsaturated fatty acids family.

In conclusion, although RPC leads to the complete resolution of the systemic inflammation after 6 months metabolic sequelae can persist. The observed low level of total and LDL cholesterol could be an index of malabsorption and was probably due to the persistency of an accelerated transit and to the exclusion of the terminal ileum caused by the covering ileostomy. The persistence of the low n-3 PUFA serum concentrations 6 months after RPC seems to suggest the presence of an intrinsic enzymatic deficiency that might play a role in colonic inflammation of patients with UC. A further analysis to clarify this point would be to evaluate the level of n-3 PUFAs in a later time after ileostomy closure.

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Pancreatic Cancer Cell Genetics and Signaling Response to Treatment Correlate with Efficacy of Gemcitabine-Based Molecular Targeting Strategies

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Abstract
Introduction Pancreatic cancer is a deadly cancer with limited sensitivity to gemcitabine. Molecular targeting of critical signaling pathways [nuclear factor kappa-B (NF-κB), PI3K/AKT, and mitogen-activated protein kinase (MAPK)] in combination with gemcitabine may improve sensitivity. We hypothesize that pancreatic cancer cell genetics and signaling response to treatment correlate with efficacy of gemcitabine-based molecular targeting strategies.
Materials and Methods PANC-1, PaCa-2, and BxPC-3 cells were treated with curcumin, LY294002, or PD325901 alone or in combination with gemcitabine. Proliferation was measured by cell counts and enzyme activity by Western blot and electrophoretic mobility shift assay.
Results Each agent dose-dependently decreased proliferation. All cells decreased NF-κB activity with curcumin(24 h) except PaCa-2, MEK activity with PD325901(24 h), and PI3Kinase with LY294002(3 h). However, PI3K rebounded to (PaCa-2) or above (Panc-1,BxPC-3) basal in LY294002-treated cells (24 h). Combinations with gemcitabine resulted in at least additive effects on proliferative inhibition. For PANC-1, curcumin + gemcitabine was nearly synergistic, correlating with gemcitabine-induced NF-κB activity. LY294002 + gemcitabine was nearly synergistic in PaCa-2 cells, which showed a lower induction of PI3Kinase activity with LY294002. Finally, gemcitabine + PD325901 was only effective in BxPC-3, which exhibited increased MEK activity with gemcitabine.
Conclusions These results demonstrate differences in treatment efficacy, which correlate with the cell's signaling response to treatment. Signaling profiles of each tumor may be necessary to determine an optimal chemotherapy for pancreatic cancer.

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Introduction

Pancreatic cancer is one of the most deadly cancers known. The estimated incidence is 37,170 new cases per year with 33,370 deaths per year.[1] The 1- and 5-year survivals are 26 and 5%, respectively.[1] Even when the disease is identified while it is confined to the pancreas, the 5-year survival is about 20%.[1] Surgery still represents the best option, but only 15% of cancers are resectable at the time of diagnosis.[2–4] The use of adjuvant chemotherapy has not improved much on survival. The use of 5-FU increased the median survival to 11–20 months.[5] Gemcitabine has been proven to be more effective, but the long-term results are still not optimal.[6]

One reason for the poor success of chemotherapy in the treatment for pancreatic cancer could be the development of resistance. There are multiple signaling pathways that could potentially enhance pancreatic cancer survival. These include nuclear factor kappa-B (NF-κB), PI3K/AKT, and mitogen-activated protein kinase (MAPK). The first of these is NF-κB, which is a transcription factor that is normally bound to the inhibitor IκB-α in the cytoplasm.[7,8] In the classical pathway, a signal is transmitted via IKK, which phosphorylates IκB-α.[7,8] This phosphorylation leads to the dissociation of NF-κB and translocation into the nucleus to exert its effects.[9] NF-κB activation leads to the production of multiple products, which are beneficial to cancer cells and may induce chemoresistance.[10–12]

The PI3K/AKT pathway is another signaling pathway that could be important in pancreatic cancer survival. PI3 kinase is activated by various extracellular signals and leads to the phosphorylation of AKT.[13] Once phosphorylated, AKT can phosphorylate a variety of proteins leading to cell survival and proliferation.[13] This is of interest, as the PI3K/AKT pathway has been found to be overactive in malignant pancreatic cancer compared to normal pancreas.[14] In addition, PI3K/AKT has been implicated in the resistance of pancreatic cancer to gemcitabine.[15,16]

Finally, the MAPK pathway is of interest as a potential target for inhibition in pancreatic cancer. In this pathway, the molecule Ras is activated and leads to the phosphorylation of Raf, which can activate MEK-1/2.[17] MEK-1/2 can then phosphorylate ERK-1/2 activating these molecules.[17] ERK-1/2 can then activate various cytosolic proteins and nuclear transcription factors.[17] This pathway has been linked to increasing chemoresistance, proliferation, and invasion in pancreatic cancer.[18,19]

Many other cell signaling pathways have been implicated in cancer proliferation and chemoresistance, but these are the three that will be investigated in this study. Each pancreatic cancer has its own genetic composition, and as such, we hypothesize that different cancer lines may develop resistance to gemcitabine (the standard chemotherapy for pancreatic cancer) based on their genetic profile and signaling response. Inhibiting these pathways should sensitize the cells to gemcitabine therapy. The purpose of this study will be to evaluate whether inhibitors to each of these pathways (curcumin, LY294002, and PD325901) will increase the effectiveness of gemcitabine as a chemotherapeutic agent.

Materials and Methods

Cells and Treatments

BxPC-3, MIA PaCa-2, and PANC-1 cells were obtained from the American Type Culture Collection (Rockville, MD, USA) and maintained as recommended. Gemcitabine (Eli Lilly, Indianapolis, IN, USA) was dissolved in sterile water and stored at 0°C. Curcumin (Sigma-Aldrich, St. Louis, MO, USA), LY294002 (Promega, Madison, WI, USA) and PD325901 (kindly provided by Pfizer) were dissolved in DMSO and stored at −20°C.

Electrophoretic Mobility Shift Assays

Cells were plated in six-well plates and grown to 50–70% confluence. The cells were incubated for 24 and 48 h with gemcitabine, curcumin, or the combination. In cases where gemcitabine was not used, TNF-α (5 ng/ml, R&D Systems) was added 10 min before harvest to stimulate NF-κB. Whole-cell lysates were incubated with radiolabeled probes specific for NF-κB or OCT-1 (Promega) as a control. DNA–protein complexes were separated by electrophoresis and visualized by autoradiography.

Western Blotting

Cells were grown in six-well plates to 70% confluence and then treated with drugs for the indicated time periods. Cells were lysed in radioimmunoprecipitation assay buffer (phosphate-buffered saline, 1% NP40, 0.5% sodium deoxycholate, 0.1% sodium dodecyl sulfate (SDS), 1 mmol/l phenylmethylsulfonyl fluoride, 10 μg/ml aprotinin, and 1 mmol/l Na3VO4), and the supernatants were obtained. Cell lysates (10 μg) were separated by SDS-polyacrylamide gel electrophoresis (PAGE) on 4 to 20% gradient gels (Invitrogen, Carlsbad, CA, USA) and transferred to Immobilon P membranes (Millipore, Billerica, MA, USA). The blots were probed with phospho-AKT, AKT, phospho-MEK, MEK, ERK, phospho-ERK (Cell Signaling Technology, Beverly, MA, USA), and

actin (Santa Cruz Biotechnology, Santa Cruz, CA, USA) according to the manufacturer's protocol. Proteins were detected with enhanced chemiluminescence (Perkin-Elmer Life Sciences, Boston, MA, USA).

Cell Counts

The cells were plated in six-well plates. Twenty-four hours later, gemcitabine, curcumin, LY294002, PD325901, or combinations with gemcitabine were added. After 72 h, trypan blue-excluded cell counts were performed. All cell counts were done a minimum of three times. Percent growth was calculated compared to the average number of cells in the control group.

Apoptosis

Apoptosis was measured using the Cell Death Detection ELISA (Roche, Indianapolis, IN, USA) according to the manufacturer's protocol. The amount of cytoplasmic histone-associated DNA fragments produced by apoptotic cells can be quantitatively determined. Relative apoptosis was determined by a ratio of the absorbance of the treatment wells to the absorbance of control wells.

Statistics

Statistical analysis was carried out using Microsoft Excel and Graphpad Prism. Statistical significance was determined using a Student's *t* test. Estimates of synergism in combination drug treatment were based on comparing the reduction in growth vs that predicted by multiplying the survival with each agent alone.

Results

Effect of Curcumin on TNF-α and Gemcitabine-Induced NF-κB Activation in Pancreatic Cancer

To determine if we could block NF-κB signaling in pancreatic cancer cells, we employed the NF-κB inhibitor, curcumin. Curcumin was administered to three human pancreatic adenocarcinoma cell lines (BxPC-3, Panc-1, and PaCa-2) after these cells had undergone TNF-α-induced NF-κB activation. Increasing doses of curcumin decreased the TNF-α activation of NF-κB as determined by NF-κB DNA binding in the Panc-1 and BxPC-3 cell lines at 24 h (Fig. 1a). This effect was most pronounced in the

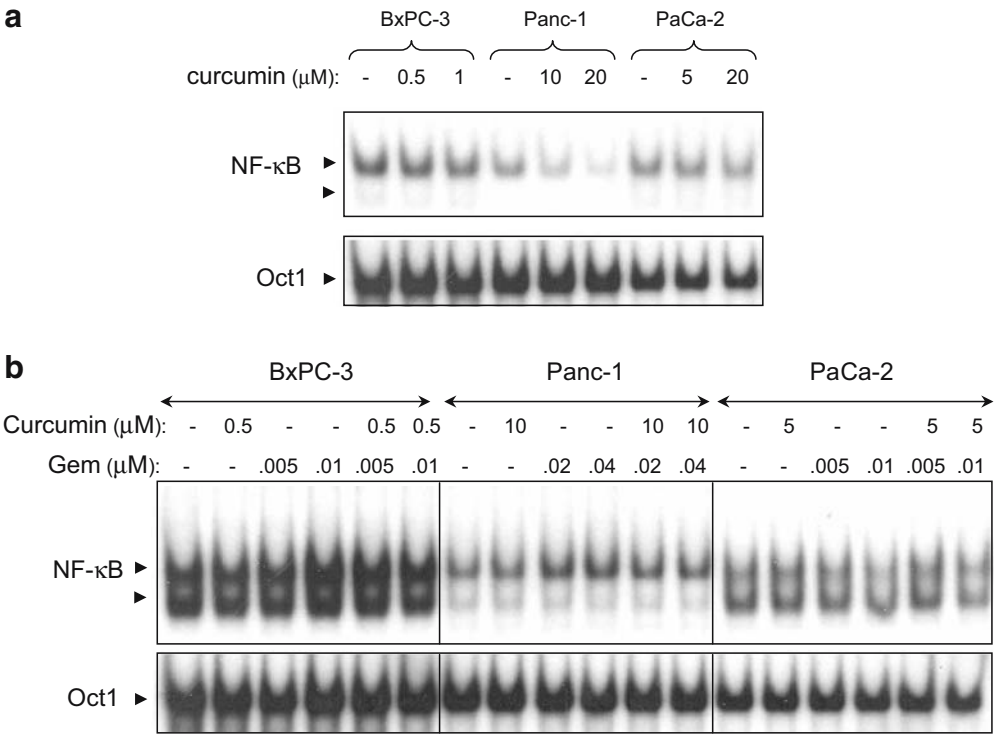


Figure 1 **a** The effect of curcumin treatment (24 h) on TNF-α evoked DNA binding of NF-κB. A representative EMSA is shown demonstrating NF-κB DNA binding in each cell line with curcumin doses that correspond to their drug sensitivity; Oct-1 binding was performed as the internal control. **b** The effect of combination treatment (48 h) on NF-κB DNA binding. A representative EMSA is shown with combinations of gemcitabine and curcumin in each of the cell lines.

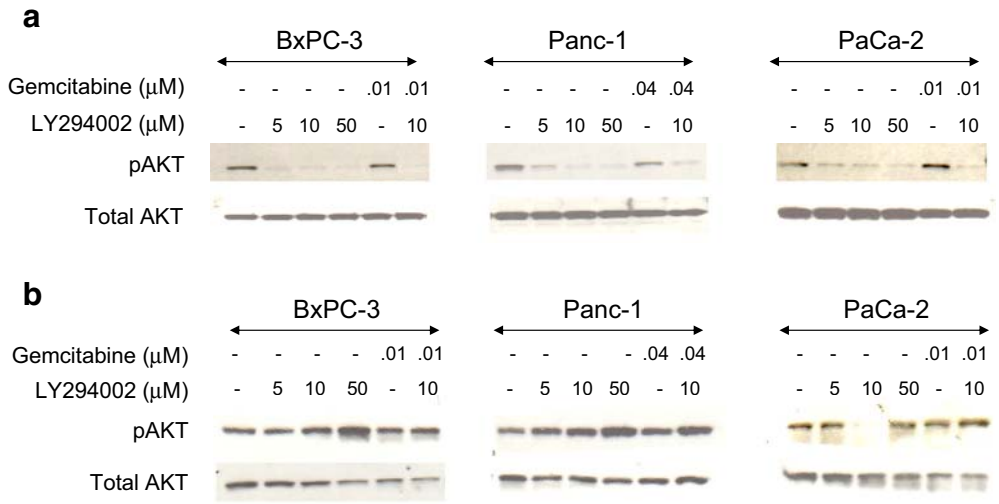


Figure 2 **a** The effect of LY294002 and gemcitabine on phospho-AKT (*pAKT*). The levels of pAKT and total AKT were determined after 30 min of treatment with LY294002 and gemcitabine in all three cell lines as shown in the representative western blot. **b** The effect of LY294002 and gemcitabine on pAKT and total AKT levels after 24 h of treatment in all cell lines. A representative Western blot is shown.

Panc-1 cell line. Curcumin did not have an effect on NF-κB DNA binding in the PaCa-2 cell line at 24 h.

To determine the effect of gemcitabine on NF-κB activity in these cell lines, we treated each of the cell lines with gemcitabine and measured NF-κB DNA binding at 48 h. Gemcitabine increased NF-κB DNA binding above basal levels in both Panc-1 and BxPC-3 cell lines (Fig. 1b). Curcumin suppressed the gemcitabine-induced NF-κB DNA binding in both Panc-1 and BxPC-3 cells. The PaCa-2 cell line did not demonstrate a change in NF-κB DNA binding with gemcitabine or curcumin treatment.

Effect of LY294002 and Gemcitabine on PI3 Kinase Activity in Pancreatic Cancer

To determine if we could block PI3 kinase activity in pancreatic cancer cells, we employed the PI3 kinase inhibitor, LY294002. PI3 kinase activity as measured by phospho-AKT (pAKT) levels was detectable in all three pancreatic cancer cell lines (Fig. 2a). All three cell lines demonstrated a decrease in pAKT after 30 min of treatment with LY294002 (5–10 μM). To determine the effect of gemcitabine on PI3 kinase activity in these cell lines, we treated each of the cell lines with gemcitabine and measured pAKT. Gemcitabine did not increase pAKT levels over baseline in any of the cell lines at 30 min (Fig. 2a). The addition of LY294002 effectively inhibited pAKT even in the presence of gemcitabine (Fig. 2a).

A longer term (24 h) effect of LY294002 on pAKT was also assessed in all cell lines (Fig. 2b). Paradoxically, both the BxPC-3 and Panc-1 cell lines demonstrated an increase in pAKT level over baseline after 24-h treatment with LY294002. The PaCa-2 cells did not demonstrate a substantial change in pAKT levels with 24 h of LY294002 treatment. The addition of gemcitabine to all cell lines had very little effect on this trend.

Effect of PD325901 and Gemcitabine on MEK Activity in Pancreatic Cancer

To determine if we could block MEK activity in pancreatic cancer cells, we employed the MEK inhibitor, PD325901.

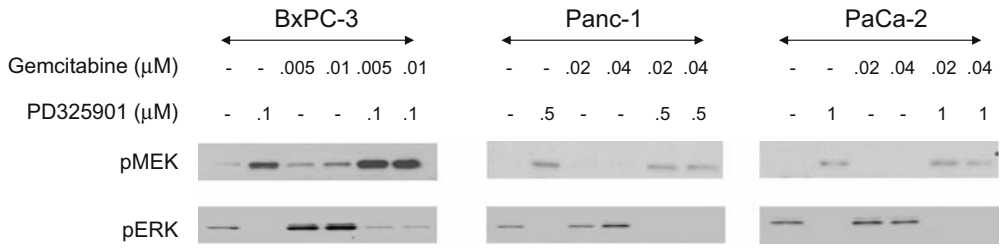


Figure 3 The effect of PD325901 and gemcitabine treatment for 24 h on phospho-MEK (*pMEK*) and phospho-ERK (*pERK*) levels. A representative Western blot is shown for all three cell lines.

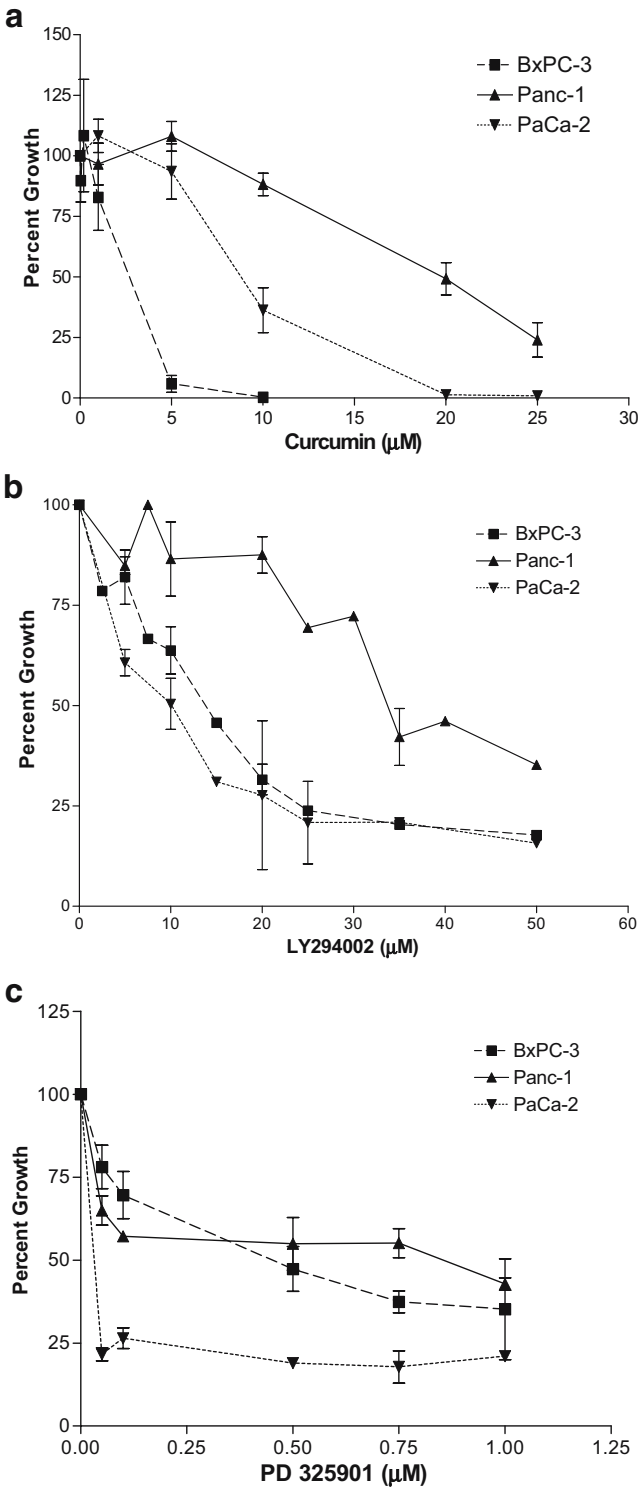


Figure 4 The effect of treatment with **a** curcumin, **b** LY294002 and **c** PD325901 on cell proliferation in BxPC-3 (*dashed lines*), Panc-1 (*solid line*) and PaCa-2 (*dotted line*) cells. Cells were treated for 72 h, and cell growth was determined by performing cell counts. *Error bars* represent the standard error of the mean.

MEK activity as measured by phospho-ERK (pERK) levels was detectable in all three pancreatic cancer cell lines (Fig. 3). The level of pERK was decreased in all three cell lines after 24 h of treatment with PD325901 (0.1–1.0 μM; Fig. 3). To determine the effect of gemcitabine on MEK activity, we treated each cell line with gemcitabine and measured pERK. Gemcitabine (0.005–0.01 μM) induced pERK in the BxPC-3 cells. Gemcitabine had little effect on pERK in the Panc-1 and PaCa-2 cell lines. The addition of PD325901 led to a decrease in pERK in all cell lines even with the addition of gemcitabine.

Upstream of MEK lies MEK kinase in the MEK-ERK pathway. MEK kinase activity was measured by phospho-MEK (pMEK) levels. Gemcitabine did not alter pMEK in the Panc-1 and PaCa-2 cell lines but led to a slight increase in the BxPC-3 cells. This explains the increase in pERK in the BxPC-3 cells. PD325901 induced pMEK in all three cell lines. This induction was relatively unchanged in the presence of gemcitabine. The drug treatments had no effect on the levels of total MEK or ERK (data not shown).

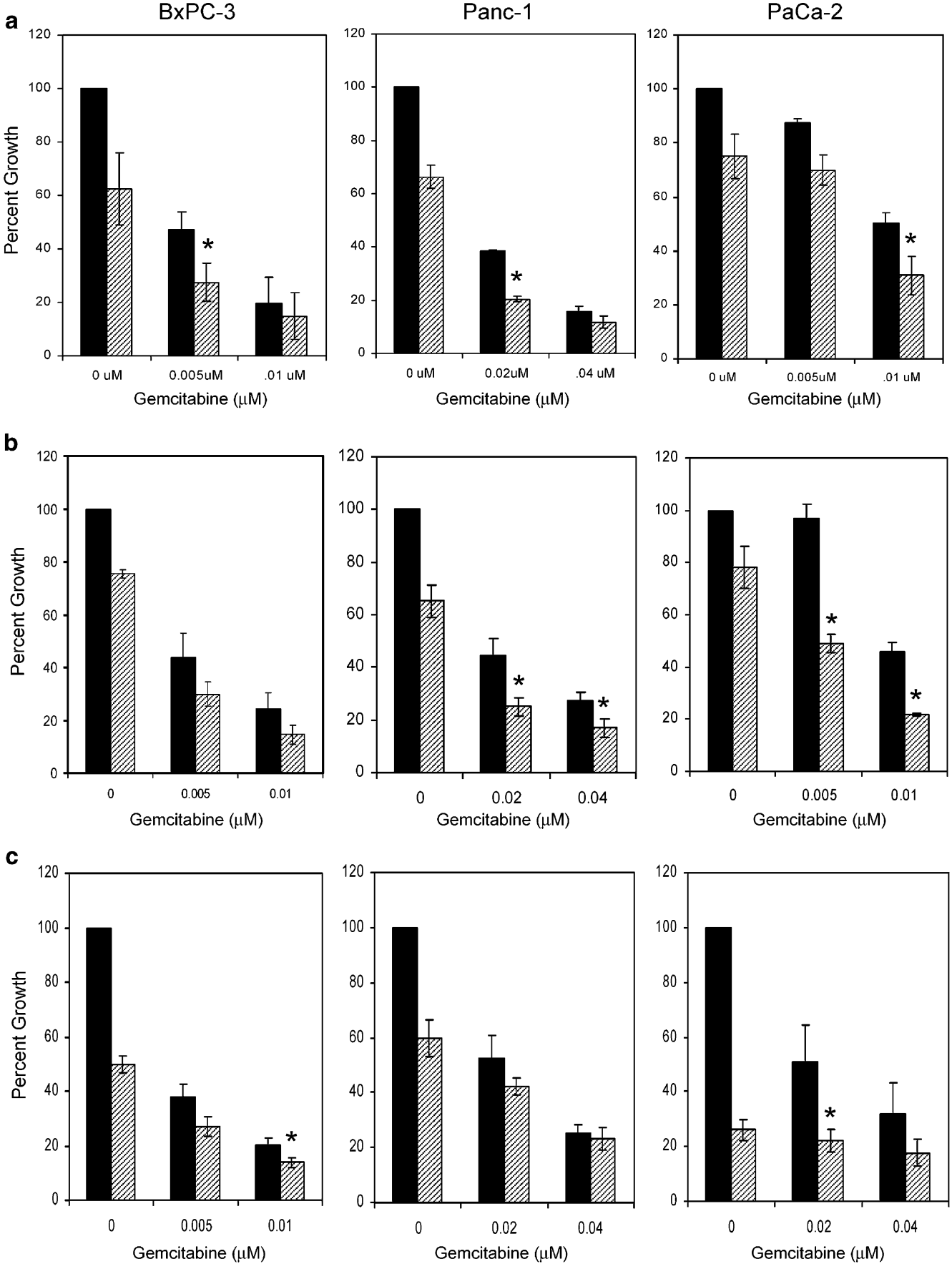
Effect of Curcumin, LY294002, and PD325901 on Pancreatic Cell Proliferation

The functional effects of targeting NF-κB, PI3 kinase, and MEK on cellular growth were measured (Fig. 4a–c). Each agent effectively caused a concentration-dependent decrease in cellular proliferation in all three cell lines. The approximate IC-50 for each drug and cell line is outlined in Table 1. BxPC-3 cells were most sensitive to treatment with gemcitabine and curcumin and relatively more resistant to LY294002 and PD325901. Conversely, the PaCa-2 cells were most sensitive to LY294002 and PD325901. Panc-1 cells were relatively resistant to all three drug treatments as demonstrated by the higher IC-50s.

Table 1 Drug Sensitivities Either Alone or in Combination with Gemcitabine

	Gemcitabine (μM)	PD325901 (μM)	LY294002 (μM)	Curcumin (μM)
BxPC-3, IC-50	0.005	0.4	15	1
BxPC-3 combination with gemcitabine		HA	A	A
PANC-1, IC-50	0.02	0.75	35	17
PANC-1 combination with gemcitabine		LA	A	HA
PaCa-2, IC-50	0.01	0.1	10	8
PaCa-2 combination with gemcitabine		LA	S	A

S Synergistic, *HA* highly additive, *A* additive, *LA* weakly additive


a
BxPC-3
Panc-1
PaCa-2
Percent Growth
120
100
80
60
40
20
0
0 uM
0.005uM
.01 uM
0.02uM
.04 uM
Gemcitabine (μM)
b
0
0.005
0.01
0.02
0.04
c

◀ **Figure 5** The effects of combining gemcitabine with **a** curcumin, **b** LY294002 and **c** PD325901. **a** The *black bars* indicate the addition of gemcitabine alone, and the *hatched bars* indicate the addition of curcumin (BxPC-3=0.5 μM, Panc-1=10 μM, and PaCa-2=5 μM). **b** The *black bars* indicate gemcitabine alone and the *hatched bars* indicate the addition of 5 μM LY294002. **c** The *black bars* indicate gemcitabine alone and the *hatched bars* indicate the addition of PD325901 (BxPC-3=0.1 μM, Panc-1=0.5 μM, and PaCa-2=1 μM). *Error bars* represent the standard error of the mean. *$P<0.05$ vs each agent alone.

Effect of Combination of Curcumin, LY294002, and PD325901 with Gemcitabine on Pancreatic Cell Proliferation

The effects of combining gemcitabine with curcumin on pancreatic cell growth are shown in Fig. 5a. In all three cell lines, the combination of gemcitabine with curcumin proved to have a statistically significant effect on decreasing proliferation of pancreatic cancer cells compared to either single agent alone. Figure 5b demonstrates the effects of combining gemcitabine with LY294002 on pancreatic cancer growth. This combination of drugs provided a significant difference over either agent alone in the Panc-1 and PaCa-2 cells. There was no advantage of this combination in the BxPC-3 cells. Figure 5c illustrates the effects of combining gemcitabine with PD325901 on pancreatic cancer growth in all three cell lines. In the BxPC-3 cells, the combination of gemcitabine (0.01 μM) and PD325901 (0.1 μM) was significant. In the PaCa-2 cells, the combination of gemcitabine (0.02 μM) and PD325901 (1 μM) was significant. There was no advantage of this combination in the Panc-1 cells.

In addition to showing the IC-50 of each drug, Table 1 indicates whether the combinations of the drugs were weakly additive, additive, highly additive, or nearly synergistic. This was determined by comparing the product of the individual agents alone compared to the observed growth of the combination. The combination of gemcitabine and curcumin was simply additive in both the BxPC-3 and PaCa-2 cell lines but was highly additive in the Panc-1 cell line. The combination of LY294002 and gemcitabine was additive in both the BxPC-3 cells and Panc-1 cells but nearly synergistic in the PaCa-2 cell line. Finally, the combination of gemcitabine and PD325901 demonstrated highly additive effects in the BxPC-3 cell line with very little effect in the other two.

Effect of Combination of Curcumin, LY294002, and PD325901 with Gemcitabine on Apoptosis

Apoptosis was measured in the cell line that was most responsive to each combination. BxPC-3, Panc-1, and PaCa-2 cells were treated respectively with gemcitabine/PD325901, gemcitabine/curcumin, or gemcitabine/LY294002 for 24 h. Apoptosis was measured by enzyme-linked immunosorbent assay (ELISA; Fig. 6). In BxPC-3 cells, although apoptosis was induced by PD325901 alone, it was not further induced by the combination. Apoptosis was not induced in Panc-1 or PaCa-2 cells by the agents alone or in combination. Similar effects were observed after 48 h of treatment (data not shown). These results suggest that the additive inhibitory

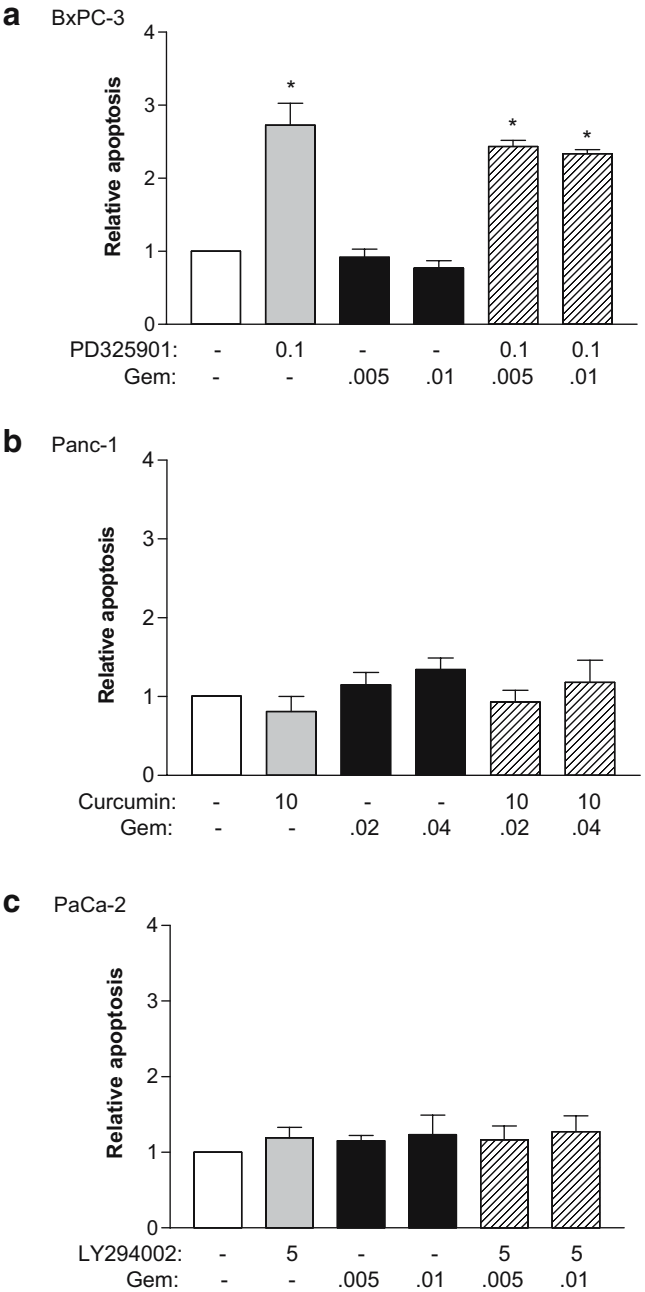


Figure 6 The effect of the agents alone or in combination on apoptosis in **a** BxPC-3, **b** Panc-1, and **c** PaCa-2 cells. After drug treatment for 24 h, the cells were analyzed for apoptosis by ELISA. Data is expressed as relative apoptosis compared to control treated cells (set equal to 1). *$P<0.05$ vs control.

effects induced by the drug combinations may be mediated by other mechanisms besides apoptosis.

Discussion

Gemcitabine is the current standard of care for adjuvant treatment of pancreatic cancer but with only marginal benefit.[6] We hypothesized that the reason for this lack of efficacy is that pancreatic cancer cells may activate cell signaling pathways that promote cell survival in the presence of chemotherapeutic agents. If this is true, blocking these pathways could sensitize the pancreatic cancer to treatment with gemcitabine. We also hypothesized that pancreatic cancer cells with different genetic composition may use different pathways to develop resistance to chemotherapy. We therefore decided to test three different signaling pathway inhibitors in combination with gemcitabine in three human pancreatic cancer cell lines.

The first pathway evaluated was the NF-κB pathway due to the large amount of data supporting this pathway as a mechanism of chemoresistance.[10–12] NF-κB also makes a logical target as it has been found to be over expressed in pancreatic cancer cells.[20] We demonstrated that gemcitabine induced NF-κB activity in BxPC-3 and Panc-1 cells; this could represent a cellular survival mechanism, which may lead to gemcitabine chemoresistance. The NF-κB inhibitor, curcumin, was able to inhibit this gemcitabine-induced NF-κB activation in both cell lines but to the greatest degree in the Panc-1 cells. Correspondingly, this combination was most effective at reducing proliferation in the Panc-1 cells, although apoptosis was not induced by the agents alone or in combination. In contrast, gemcitabine did not induce NF-κB activity in PaCa-2 cells. Furthermore, curcumin alone did not inhibit NF-κB activity in PaCa-2 cells. Previous studies from our laboratory have demonstrated an alternative NF-κB inhibitor, parthenolide, effectively decreased NF-κB activity in the PaCa-2 line; however, parthenolide failed to sensitize PaCa-2 cells to gemcitabine (unpublished observations).[21] Surprisingly, curcumin increased the sensitivity of PaCa-2 cells to gemcitabine despite showing no gemcitabine-induced NF-κB activation. This may be explained by other effects curcumin has on the cell including the inhibition of AKT, JNK, and ERK.[22]

We next examined the PI3K/AKT pathway, which is active in a large number of malignant pancreatic cancers.[14] In addition, Ng. et al.[15] demonstrated that inhibiting the PI3K/AKT system in PK1 and PK8 cells increases gemcitabine induced apoptosis. The drug LY294002 was chosen to inhibit the PI3K/AKT pathway in this study. We showed that the PI3K/AKT inhibitor, LY294002, suppressed cell growth in all three cell lines with Panc-1 cells having the highest IC-50 and PaCa-2 cells the lowest. Interestingly, although LY294002 was effective at early time points, pAKT levels rebounded at later time points. In PaCa-2 cells, the level of pAKT rebounded to basal level and in BxPC-3 and Panc-1 cells to above the basal levels. This may be a cell survival mechanism, compensating for inhibition of the PI3K/AKT pathway.

Gemcitabine treatment alone did not induce pAKT. Therefore, the effectiveness of gemcitabine combined with PI3K/AKT targeted agents cannot be explained in the same way as gemcitabine combined with NF-κB targeted agents. The combination of gemcitabine and LY294002 produced statistically significant additive effects in both the Panc-1 and PaCa-2 cells. This was most pronounced in the PaCa-2 cells although the agents either alone or in combination did not induce apoptosis. The Panc-1 and PaCa-2 cells produce higher basal levels of AKT than the BxPC-3 cells do.[23] These data are also supported by Shah et al.[24] who demonstrated that LY294002 enhanced TNF-α induced antiproliferation in Panc-1 and PaCa-2 cells. From our study, the PaCa-2 cells demonstrated the smallest rebound of pAKT levels after LY294002 treatment. Correspondingly, they were the most sensitive to LY294002 alone or in combination with gemcitabine. Thus, treatment response was mainly dictated by signaling response to LY294002 with this combination.

The final pathway that was evaluated in this study was the MEK-ERK pathway. This pathway was chosen, as it has been implicated in resistance to gemcitabine in pancreatic cancer.[18] In addition, MEK inhibitors have been demonstrated to inhibit pancreatic cancer proliferation and invasion that is normally stimulated by glial-derived neurotrophic factor.[19] We demonstrated that targeting MEK activity with PD325901 inhibited the phosphorylation of ERK and cell growth in all cell lines. Gemcitabine induced activated MEK (pMEK) and ERK (pERK) exclusively in the BxPC-3 cells. We hypothesized that this may represent a cellular survival mechanism, which could lead to gemcitabine chemoresistance. Correspondingly, gemcitabine combined with PD325901 produced additive antiproliferative effects in the BxPC-3 and PaCa-2 cell lines. These effects were most pronounced in the BxPC-3 cells. Although PD325901 alone induced apoptosis in BxPC-3 cells, the combination did not further induce apoptosis. Furthermore, the BxPC-3 cell line is the only one of the three cell lines used that expresses wild-type K-ras. It might be predicted that the mutant K-ras would lead to higher levels of MEK activation, but Brown et al.[8] actually demonstrated higher rates of MEK activation in non-mutant K-ras pancreatic cancers. That study hypothesized that normal K-ras pancreatic cancers may actually have another method of activating the MEK system.[8] MEK based chemoresistance to gemcitabine mirrors NF-κB based chemoresistance to gemcitabine in so far as the most sensitive cells tend to be those where gemcitabine increases the activity of the

signaling pathway the most. Direct evidence linking induction of MEK and NF-κB with chemoresistance will require overexpression studies, which are currently ongoing in our laboratory.

Conclusion

These data demonstrate that the BxPC-3, Panc-1, and PaCa-2 human pancreatic cancer cell lines have unique responses to different intracellular signaling pathway inhibitors in combination with gemcitabine. The optimal agent combined with gemcitabine enhances antiproliferative effects on the pancreatic cancer cells. Our in vitro study of the intracellular signaling response to gemcitabine and knowledge of the genetics of each cancer helped determine the best treatment combination with gemcitabine for a particular pancreatic cancer. Ideally, operative biopsies of patient's cancers may be used to type the cancer's genetics and signaling response to chemotherapy in vitro such that combination treatments can be effectively discovered in clinical practice.

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Right Portal Vein Ligation is as Efficient as Portal Vein Embolization to Induce Hypertrophy of the Left Liver Remnant

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Abstract
Background Aim of this retrospective study was to compare induction of left liver hypertrophy after right portal vein ligation (PVL) and right portal vein embolization (PVE) before right hepatectomy for liver metastases.
Materials and Methods Between 1998 and 2005, 18 patients underwent a PVE, whereas 17 patients underwent a PVL during a first stage laparotomy.
Results There was no complication related to PVE or PVL. After a similar interval time (7±3 vs 8±3 weeks), the increase of the left liver volume was similar between the two groups (35±38 vs 38±26%). After PVE and PVL, right hepatectomy was performed in 12 and 14 patients, respectively. Technical difficulties during the right hepatectomy were similar according to duration of procedure (6.4±1 vs 6.7±1 h, $p=0.7$) and transfusion rates (33 vs 28%, $p=0.7$). Mortality was nil in both groups, and morbidity rates were respectively 58% for the PVE group and 36% for the PVL group ($p=0.6$).
Conclusion Right PVL and PVE result in a comparable hypertrophy of the left liver. During the first laparotomy of a two-step liver resection, PVL can be efficiently and safely performed.

Keywords Portal vein occlusion · Portal vein ligation · Liver metastasis · Liver hypertrophy

Abbreviations
PVL portal vein ligation
PVE portal vein embolization
FLR future liver remnant

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Introduction

In patients with primary liver tumors or selected liver metastases, complete resection is often the only chance of potential curative treatment to expect a long-term survival.[1,2] In case of extended hepatic lesions, liver resection may be hampered by the small volume of the residual liver, which is associated with a risk of postoperative life-threatening liver failure.[3,4] Moreover, many patients with advanced metastatic disease are referred to surgeons after a neoadjuvant chemotherapy, which has allowed downsizing of initially unresectable liver metastases,[5] or when there is a documented chemosensitivity.[6,7] Now, it has been well established that chemotherapy induces liver parenchyma changes, which may worsen postoperative morbidity.[8,9] In patients considered for liver resection of metastasis, both small volume of the future remnant liver and neoadjuvant chemotherapy increase the postoperative morbidity and mortality risk.

To overcome this risk and to increase resectability, more aggressive surgical treatment procedures have been proposed using the regenerative capacity of the liver.[10,11] Among them, occlusion of one branch of the portal vein

results in the atrophy of the ipsilateral and hypertrophy of the contralateral liver segments. This phenomenon was initially observed in patients with cholangiocarcinoma, which induced portal vein occlusion by tumor invasion.[12] Including portal vein occlusion in a strategy of scheduled sequential liver resections allowed to increase the number of patients amenable to curative surgery, while they were initially deemed unresectable.[10,11,13] Portal vein occlusion may be achieved by either percutaneous embolization or surgical ligation during a first-step laparotomy. Right portal vein ligation (PVL) has been considered to be less efficient than right portal vein embolization (PVE) before a right hepatectomy.[14,15]

The present study aimed to compare PVL and PVE before a right hepatectomy in patients with liver metastases in terms of safety, efficacy for hypertrophy of the left liver remnant, resectability rates, and technical impact on liver resection.

Materials and Methods

Patients

Between 1998 and 2005, 35 patients with multiple colorectal or neuroendocrine liver metastases underwent a right portal branch obstruction before "high risk" right hepatectomy because of a future liver remnant (FLR) volume less than 30% of the total liver volume or because of a post-chemotherapy liver parenchyma. Eighteen patients underwent a percutaneous PVE because metastases were considered resectable in one stage. Seventeen patients had a PVL during a first-stage laparotomy when the metastatic disease in the left liver was judged too extensive to be safely resected along with the right liver (n=10) and/or when the resection of the primary tumor was also required (n=10). Patients and tumors characteristics are given in Table 1. In the PVE group, patients were older than in the PVL group (51±10 vs 61±14 years, respectively, p=0.023), and all patients had colorectal metastases, whereas ten (59%) patients had neuroendocrine metastases in the PVL group (p=0.02). There were more hepatic lesions, and they were bigger in the PVL group. Liver function assessed by prothrombin time, and bilirubin was normal and comparable in both groups (data not shown). Neoadjuvant chemotherapy consisting in the combined use of 5-fluorouracil and either oxaliplatin or irinotecan was administrated to all patients before PVE and to eight (47%) patients before PVL (p=0.001). Mean time between the end of chemotherapy and portal vein occlusion was 2.2±1.7 months and was not significantly different between groups.

Right Portal Vein Embolization

Right PVE was performed using the contralateral transhepatic approach as previously described.[16] In brief, a collateral vein of the left branch of the portal vein was punctured under light general anesthesia and ultrasound guidance. After control venous portography, the right anterior and posterior portal branches were embolized with a mixture of cyanoacrylate (Histoacryle; Braun Lab, Hamburg, Germany) and lipiodol (Lipiodol Ultrafluide; Guerbert Lab, Paris, France). In none of them, branches to segment 4 were embolized. Control portography was performed at the end of the procedure.

Right Portal Vein Ligation

Ligation of the right branch of the portal vein was performed as part of a two-stage procedure.[10] During the first stage, the resection of the primary tumor was performed in ten patients (one left colectomy, two ileocolic resections, and seven left pancreatectomies), and enucleation of the left-sided liver metastases, with at least a 5-mm margin, was achieved in 16 patients. Extraparenchymal ligation of the right portal branch was performed using a nonabsorbable suture. Its efficacy was checked by preoperative Doppler ultrasounds. Cholecystectomy was performed in the same time in ten patients.

Table 1 Characteristics of Patients Who Underwent PVE or PVL Before Right Hepatectomy for Liver Metastases

	PVE (n=18)	PVL (n=17)	p value
Gender (F/M)	7/11	10/7	0.3
Age (year)	61±10	51±14	0.023
Primary tumor			
Adenocarcinoma	18	7	0.001
Neuroendocrine	0	10	
Hepatic tumor location unilobar/bilobar	12/6	1/16	0.03
No. of tumors/patient			
Right liver	4.5±6	7±3	0.05
Left liver	0.5±0.7	3.2±2	0.001
Preoperative chemotherapy (%)	18 (100)	8 (47)	0.001

Continuous variables expressed as mean±SD

Right Hepatectomy

Right hepatectomy was performed 7 to 8 weeks after portal vein occlusion. All patients underwent liver resection by three senior liver surgeons, using a standardized technique for right hepatectomy.[16] Parenchymal transection was performed by either the clamp-crush technique or with an ultrasound aspiration dissector (Dissectron™; Satelec Medical, Merignac, France), with intermittent clamping of the hepatic pedicle. Patients were routinely transferred to the intensive care unit and returned to the wards at the discretion of the intensive care consultant. After right hepatectomy, the resected specimens were examined pathologically, paying attention to the disease-free margins and to the extent of necrosis of tumor. Tumor necrosis was defined as complete if no viable cells were observed in any nodule.

Follow-up and End Points

The primary end point of the analysis was the hypertrophy of the FLR induced by the right portal vein occlusion. All patients underwent volumetric helicoidal computed tomographic (CT) scan estimation of their liver volumes before the obstruction and 4–6 weeks thereafter. Measurements were performed for the whole liver and for the FLR using the middle hepatic vein, gallbladder bed, and umbilical portion of the left portal vein as landmarks. The FLR volume was expressed as a percentage of the total liver volume, excluding the tumor volume. Its hypertrophy after portal vein occlusion was calculated as follows: (FLR volume 4 to 6 weeks after portal vein obstruction−FLR volume before portal vein obstruction)×100/FLR volume before portal vein obstruction.

The secondary end points of the analysis were the resectability rate and the postoperative course. Operative mortality was defined as death occurring within the same hospital stay or within 30 days of surgery. Postoperative complications, recorded prospectively, were defined as follow: (a) liver failure was defined by a prothrombin time of less than 50% (of normal) and serum bilirubin level greater than 50 μmol/l on postoperative day 5,[17] (b) significant ascites (abdominal drain output more than 500 ml/day), (c) biliary leak as the presence of bile in the abdominal drainage or abdominal collections greater than twice the serum level, (d) postoperative pulmonary complications included all clinically symptomatic pleural effusions, atelectases, and infections, and (e) renal insufficiency (serum creatinine level greater than 150 μmol/l).

Statistical Analysis

Summary statistics are expressed as mean±SD unless otherwise stated. Continuous variables were compared using the Fisher's exact *t* test, and categorical variables were compared using the Mann–Whitney test. A *p* value of less than 0.05 was considered as statistically significant. All the calculations were performed with the Statistical Package for the Social Sciences (SPSS) 14.0 statistical package (SPSS, Chicago, IL, USA).

Results

Liver Hypertrophy

Right portal vein occlusion was complete in all the cases in both groups. The mean interval time between portal vein occlusion and liver resection was similar in both groups (7±3 after PVE vs 8±3 weeks after PVL, $p=0.6$). The left liver volume increased from 509±222 ml to 641±220 ml after PVE ($p<0.001$) and from 477±179 to 638±192 ml after PVL ($p<0.001$). After portal vein occlusion, the increase of the left liver volume was not significantly different between the two groups (35±38% after PVE vs 38±26% after PVL, $p=0.7$; Fig. 1). None of the tumor but one in the left lobe increased until surgery (see below).

There was no complication after PVE and postoperative hospital stay was 2±1 days. In group PVL, four patients had postoperative complications (one left pleural effusion, two pancreatic fistulae, and one intra-abdominal abscess), which were all related to primary tumor resection, and postoperative hospital stay was 13±6 days.

Resectability

After PVE, six (30%) patients were not eligible for right hepatectomy because of insufficient hypertrophy of the left liver ($n=2$) or tumor progression ($n=4$). Two patients had peritoneal implants at laparotomy, one patient developed mediastinal metastatic lymph nodes, and in the last patient, diameter of the left lobe metastasis increased from 4 to 7.5 cm.

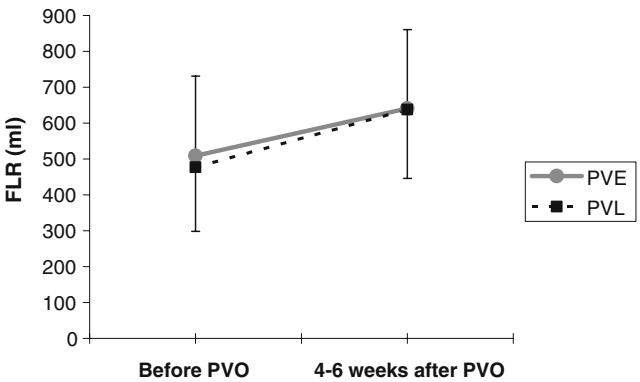

Figure 1 Volume of the future liver remnant (*FLR*) before and 4–6 weeks after portal vein embolization (*PVE*) or portal vein ligation (*PVL*). *PVO* Portal vein occlusion.

After PVL, three (18%) patients were not eligible for resection. Two patients developed tumor progression, which were lung metastases and metastatic lymph nodes in the hepatic ligament. One patient died from cardiac infarction before the second-step laparotomy. The difference of resectability between groups was not significant.

According to the pathologic examination, the maximum tumor diameter was measured as 6.5±4 cm in the PVE group and 4.8±3.7 cm in the PVL group (p=0.5). The amount of tumor necrosis was 47±29% in group PVE and 43±43% in group PVL (p=0.6). Liver parenchyma lesions induced by chemotherapy (sinusoidal dilatation, steatosis, and nodular regenerative hyperplasia) were found in six patients after PVE and in five patients after PVL (p=0.72).

Intra- and Postoperative Course

Technical difficulties during surgical procedure were similar in both groups according to duration of procedure, blood loss, and transfusion rates after PVE and PVL, respectively (Table 2). Before resection, CT scan showed stigmata of portal cavernoma in three patients of each group. However, these vein dilatations did not make right hepatectomy more difficult. After PVL, previous cholecystectomy was not associated with more technical difficulties to perform right hepatectomy. There was no significant difference between patients with (n=8) or without cholecystectomy (n=6) in terms of duration of procedure (6.1±1.6 vs 6.3±0.5 hours, p=0.8), blood loss (775±872 vs 1025±464 ml, p=0.6) and transfusion rates (33 vs 25%, p=0.9).

The mortality after right hepatectomy was nil in both groups. The overall morbidity rate was 33%. Morbidity rates were respectively 58% for the PVE group and 36% for the PVL group (p=0.6), and the numbers of complications were 11 for the PVE group and 8 for the PVL group (Table 2). Hospital stay was not significantly different between both groups (24±20 vs 19±13 days after PVE and PVL, respectively, p=0.5).

Discussion

Results of the present study, which confirms that preoperative right portal occlusion induces significant hypertrophy of the future left remnant liver, showed that right PVL is as efficient than right PVE for inducing preoperative hypertrophy. Furthermore, PVL did not result in more preoperative difficulties during the second-step hepatectomy or more postoperative morbidity.

Serial CT scans allowed to establish well that PVE leads to macroscopic atrophy of the embolized liver and hypertrophy of the contralateral lobe. At the cellular level, some studies in humans support that both hypertrophy and replication are responsible for volume enlargement of the non-embolized liver after PVE, whereas both hepatocyte atrophy and apoptosis, predominantly in the perivenular area, lead to a decrease in volume of the embolized liver.[18–20] As the portal flow is presumed to have a hepatotrophic effect,[21,22] there is rational to get the most complete occlusion of a portal territory to expect the most effective hypertrophy of the contralateral liver lobe.

In patients with synchronous bilobar liver metastases that could not be completely resected within a single hepatectomy because of a small-anticipated residual liver volume, a two-step liver resection has been proposed.[10,11,13] The first step includes resection of metastases located in one liver lobe followed, several weeks later, by a second procedure with, in most cases, a contralateral liver lobe resection (Fig. 2). This strategy allows curative resection in patients who would otherwise be contraindicated for liver surgery.[11,13] The safety of the second procedure is facilitated by the hypertrophy of the FLR, which could be enhanced by a PVL during the first-step procedure or by a PVE after the initial procedure. In our previous experience of two-step strategy including PVL during resection of the primary tumor and/or clearance of left liver metastasis, we experienced evident volume increase of the non-ligated liver allowing us to perform safely right

Table 2 Intraoperative Characteristics and Postoperative Complications After Right Hepatectomy in PVE (n=12) and PVL (n=14) Groups

	PVE (n=12)	PVL (n=14)	p value
Intraoperative course			
Operating time (hours)	6.3±1.8	6.1±1.3	0.8
Intraoperative blood loss (ml)	1354±1837	900±660	0.5
Transfused patients (%)	4 (33)	4 (28)	0.7
No. of cavernoma	3	3	0.8
Postoperative complications			
No. of patients with complications (%)	7 (58)	5 (36)	0.6
Ascites	4	2	
Hepatocellular failure	2	2	
Pulmonary complications	3	2	
Renal failure	1	0	
Intraabdominal collections	1	2	

Continuous variables expressed as mean±SD

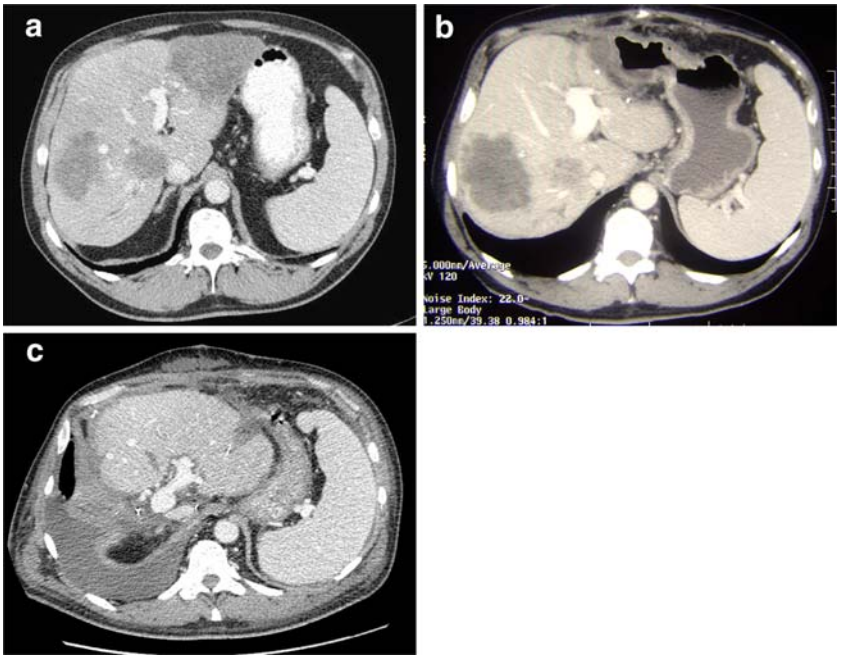

Figure 2 **a** A computed tomography scan in a 56-year-old patient who developed synchronous bilobar colorectal metastases and was treated by left colectomy and 6-month systemic chemotherapy. **b** Six weeks after resection of the left lobe tumor and right portal vein ligation, the volume of the left liver remnant increased while the right liver atrophied. **c** The residual liver 10 days after right hepatectomy.

hepatectomy.[10] As there is still a debate whether PVL is as efficient as PVE, this retrospective study aimed to compare PVL and PVE in terms of efficiency to induce hypertrophy of the FLR volume and impact on the planned liver resection after portal vein occlusion.

Broering et al.,[15] comparing PVE and PVL for induction of hypertrophy of the left lateral lobe before extended right hepatectomy, showed that PVE was more efficient. However, in the latter study, 60% of patients who underwent PVE had a partial or complete occlusion of the segment IV branches, whereas 29% in the PVL group (p=0.02). In our experience, we do not embolize segment IV branches to avoid migration of cyanoacrylate in the left portal branch, which would compromise the second-step hepatectomy. Results of the present study are consistent with those from Bouzari et al.[23] Their results confirm that PVL is as effective as PVE in inducing hypertrophy of the FLR volume. PVL was supposed to be less efficient than PVE because it may induce the formation of intrahepatic porto-portal collaterals leading to failure of liver hypertrophy.[14] However, in an experimental model, Krupski et al.[24] showed that the increase of liver volume after PVL was not restrained by the formation of porto-portal collaterals. The fortnight normalization of increased portal blood flow induced by portal vein occlusion in humans[25] and the early peak of hepatocyte proliferation after portal occlusion in rodents[26,27] suggest that liver hypertrophy is early induced after portal occlusion. Then, later formation of porto-portal collaterals would not impact on the induced liver hypertrophy. In this way, a recent experimental study in a non-human primate model supports that even a reversible portal vein occlusion may act as a starter for the liver hypertrophy.[28]

Another important result of the present study is that PVL did not result in more perioperative difficulties during the second-step hepatectomy or more postoperative morbidity. The second-step right hepatectomy were performed with a zero mortality rate and a 33% overall morbidity rate, which are consistent with the literature.[2,29,30] According to operating time, blood loss, and transfusion rates, perioperative technical difficulties during second-step hepatectomy in the PVL group were not affected by the presence of portal collaterals, previous liver resection, and cholecystectomy. We think that attention should be directed toward safe and complete left liver resection without unnecessary dissection or mobilization that could impact the difficulty of the second step. Excessive dissection of the porta hepatitis should be avoided to facilitate redissection at the second procedure. Cholecystectomy, which could be necessary to allow efficient control of the right branch of the portal vein, seems to have no impact on the technical difficulties.

In the present study, we were able to perform the scheduled second-step right hepatectomy in 74% of the patients. This figure is comparable with other series of two-stage hepatectomy from the literature, which report 55–85% resectability rates.[13,15,31] This rate was 82% after PVL and 67% after PVE, but the difference did not reach significance. This difference could be explained by a more important severity of colorectal cancer than neuroendocrine cancer. Interestingly, no PVL patient was precluded

from second-step hepatectomy because of an inadequate left liver hypertrophy.

There is evidence to suggest that portal vein occlusion may stimulate tumor growth in both the embolized and non-embolized lobes of the liver.[31,32] Elias et al.[31] reported patients whom liver metastases of the non-embolized lobe grew more rapidly that the liver parenchyma. In our series, except for one patient, there was no significant increase of left liver metastases volume after PVE. No any new lesions appeared in the left liver after portal occlusion in both groups. In this context of suspicion of tumor growth induced by portal vein occlusion, patients with PVL may benefit from this procedure, as clearance of the contralateral lobe may be achieved in the same time. Thus, 16 of the 17 PVL patients had local resection of the left-sided liver metastases. Of note, the only patient in whom left-side metastasis growth precluded the second-step liver resection had a PVE.

We are aware that indications for portal vein occlusion could be debated and that the two groups are not similar. Indications for portal vein occlusion depend on factors that impact the FLR volume needed for adequate post-hepatectomy liver function in an individual patient. Presence or absence of underlying liver disease, patient size, and the extent and complexity of the planned resection must be considered in the setting of the patient's comorbidities, which may affect hepatic regeneration. As guidelines for portal vein occlusion are continuously evolving[33] and impact of intensive chemotherapy on postoperative course is still not very well known,[34] we chose to perform portal vein occlusion in patients who have received intensive chemotherapy and/or who were planned for significant resections in the left liver lobe before a right hepatectomy.

In the PVL group, the primary tumor was either a neuroendocrine tumor (59%) or a colorectal adenocarcinoma with advanced liver metastases (41%), whereas all patients in the PVE group were referred for colorectal liver metastases, the colorectal primary tumor being previously resected. That is the reason why the PVL patients were younger, and more patients in the PVE group received chemotherapy at the time of referral. We recently showed that continuing chemotherapy while portal vein obstruction is performed did not impair the hypertrophy of the FLR volume.[35] Furthermore, liver parenchyma lesions induced by chemotherapy were found in only six PVE and five PVL patients. Finally, the rate of liver hypertrophy in the PVE group (35%) correlates well with previous reports from literature,[3,4,11,32,35] which suggest that neither older age of patients nor chemotherapy administration would have minimized the effect of PVE and the difference with PVL-induced hypertrophy. The PVL patients were younger and had more numerous tumors, which were bigger and bilobar with a primary cancer to be resected, whereas PVE patients were referred with colorectal metastases in the context of a small-anticipated residual liver volume. This point particularly expresses the fact that the two procedures may be applied in different indications or strategies but with the same efficiency in term of hypertrophy of the liver. Patients with multiple liver metastases, an inadequate residual liver, and a synchronous primary cancer may benefit from PVL.

In conclusion, results of this study clearly showed that right PVL and PVE result in a comparable hypertrophy of the left liver. Therefore, during the first laparotomy of a two-step liver resection, PVL can be safely performed, as it induces efficient hypertrophy of the left liver and does not adversely impact postoperative course.

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Effect of Laparoscopic Fundoplication on Hypertensive Lower Esophageal Sphincter Associated with Gastroesophageal Reflux

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Abstract For hypertensive lower esophageal sphincter with dysphagia and chest pain, a laparoscopic cardiomyotomy is recommended. Recently, the role of gastroesophageal reflux in this abnormality has been recognized. A prospective study on six patients with manometrically proven hypertensive lower esophageal sphincter was performed. Laparoscopic floppy Nissen fundoplication was performed in all cases. The first follow up was performed 6 weeks after the operation. The mean follow up time was 56 months (range 50–61). Before the operation, all patients had abnormal esophageal acid exposure. Mean DeMeester score was 41.7 (range 16.7–86). Average LES pressure before the operation was 50.5 mmHg (range 35.6–81.3). Six weeks after operation, all patients were symptom free. DeMeester score returned to a normal level of 2.9. Furthermore, a marked decrease in the lower esophageal sphincter pressure (24.7 mmHg) was detected. At late follow up, all patients were symptom-free, and only two patients agreed to undergo functional testing. The mean DeMeester score of this two patients was 1.2. The pressure remained at normal value (15.7 mmHg). In our study, an antireflux operation normalized lower esophageal sphincter pressure suggesting that abnormal esophageal acid exposure may be an etiologic factor in the development of hypertensive lower esophageal sphincter.

Keywords Hypertensive lower esophageal sphincter · Gastroesophageal reflux disease · Laparoscopic Nissen fundoplication

Introduction

It is well known that one of the most important factor in the pathogenesis of gastroesophageal reflux disease (GERD) is the insufficient pressure of lower esophageal sphincter (LES). This can be due to an inadequate overall or intraabdominal length of the sphincter and/or hypotension of LES. Therefore, the association between GERD and hypertensive lower esophageal sphincter (HLES) has always seemed paradoxical. HLES was first described by Code et al in 1960.[1] It is classified as a primary esophageal motility disorder and characterized by a high resting pressure of LES, which exceeds the upper limit of LES pressure measured in normal population. It is distinguished from diffuse esophageal spasm and achalasia, which also presented with elevated pressure of LES, by normal esophageal body motility and LES relaxation. The most common symptoms in patients with HLES are dysphagia and chest pain [2–4], and therefore, therapy was mostly focused on decreasing the pressure of LES by surgical or medical means. Recent reports showed that HLES can also be associated with symptoms of GERD and abnormal esophageal acid exposure, measured by 24-h pH monitoring.[5,6] Therefore, therapy recommendation for reducing sphincter pressure raises questions of worsening gastroesophageal acid reflux. On the other hand, therapy for

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abnormal acid exposure with a fundoplication carries a possible risk of more severe obstructive symptoms. Our very first patient with HLES had abnormal gastroesophageal acid reflux on pH monitoring with typical symptoms of GERD. We performed a laparoscopic cardiomyotomy with Dor fundoplication. One year later, reflux symptoms of the patient worsened, and abnormal esophageal acid exposure on pH monitoring remained. A revisional Nissen fundoplication then had to be performed. This experience led us to perform a prospective study on patients with HLES associated with GERD to evaluate the effect of laparoscopic fundoplication.

Materials and Methods

Overall Patients' Characteristics

Between January 1999 and 2006, a total of 222 patients underwent laparoscopic fundoplication for GERD. Out of them, six patients had GERD associated with HLES. Inclusion criteria were HLES detected by stationary manometry and typical symptoms of GERD. Patients with achalasia or other esophageal motility disorders were excluded. All patients underwent endoscopy, 24-h esophageal pH monitoring, stationary esophageal manometry, and barium swallow as well. There was no disturbance in esophageal clearance on barium X-ray. Out of the six patients who entered the study, there were five women and one man with a mean age of 40.5 years (range 19–74). Four patients had endoscopic signs of esophagitis and 3 presented with a hiatal hernia. In all patients, laparoscopic floppy Nissen fundoplication was performed. No intra- and perioperative morbidity was observed. There was no mortality. Patients were first called back for manometry and 24-h pH monitoring 6 weeks after the operation. Then, they were yearly followed by symptom questionnaire and barium swallow. At later follow-ups, patients who agreed underwent 24-h esophageal pH monitoring and stationary esophageal manometry. The mean follow up time was 56 months (range 50–61). At late follow-up, only two patients agreed to undergo functional testing.

Stationary Esophageal Manometry

Esophageal manometry was performed with a water perfused catheter system (perfusion manometry and portable data recording system, Medtronic, Sweden), using a catheter with 0.8 mm opening located 5 cm apart and a perfusion rate of 0.5 ml/min. HLES was defined if the pressure of LES was above 35 mmHg (>95th percentile of normal population), relaxation of LES was normal, and no esophageal body motility disorder was present.

24-h Esophageal pH Monitoring

All medicaments, which interfere with acid production were discontinued 2 weeks before the measurement. After an overnight fast, 24-h esophageal pH monitoring was performed (portable pH recording system, Medtronic, Sweden) by placing an antimony multi-use electrode, 5 cm above the upper border of the manometrically determined LES. After 24 h of measurement, the probe was removed and data were downloaded into a computer and analyzed using a commercial software (Polygram, Medtronic, Sweden). DeMeester score was used to define the esophageal acid exposure.

Symptom Assessment

Symptoms were assessed by one of the surgeons. A structured questionnaire for foregut symptoms was performed. Regurgitation, heartburn, and epigastric pain were scored as follows: 0 (none); 1 (weekly once); 2 (twice a week); 3 (three times a week); 4 (four times a week); 5 (daily). Dysphagia was graded as 0 (none), 1 (occasionally with solid food, lasting for a few minutes), 2 (once a week, requiring clearing with fluids), 3 (more than once a week), 4 (dysphagia to semi liquid foods), and 5 (dysphagia to liquids). The patients with HLES were included only if three major symptoms of GERD (regurgitation, heartburn, epigastric pain) were present and the score was above 3. Dysphagia as minor symptom (score 0 or 1) was no reason for exclusion.

Results

24-h Esophageal pH Monitoring

Before the operation the mean DeMeester score was 41.7 (range 16.7–86). Six weeks after surgery the score returned to a normal value of 2.9 (range 0.3–4.1). At late follow-up, only two patients agreed to undergo 24-h pH monitoring. The mean DeMeester score was 1.2.

Stationary Esophageal Manometry

The mean pressure of LES was 50.55 mmHg (range 35.6–81.3) before surgery. After the operation, the average LES pressure was 24.7 mmHg (range 23.2–26.6) at 6 weeks and 15.7 mmHg at late follow-up.

Symptoms

Besides major symptoms of reflux, two patients also had a slight dysphagia. Although the pressure of LES was higher in the two patients who had dysphagia besides their reflux

symptoms, there was no significant difference regarding to LES pressure (54.8 vs 48.4) or DeMeester score (41.5 vs 41.9) between the two patients with slight dysphagia and the other four without dysphagia. The only difference was that the two patients with dysphagia had the more severe esophagitis on endoscopy, and they both had a hiatal hernia. No chest pain was observed before the operation. Six weeks after the operation, all patients were symptom-free. No new onset dysphagia or chest pain developed in the first year of follow-up. The dysphagia, in two patients who had minor dysphagia before the operation, was also resolved. One patient developed dysphagia 2 years after surgery. He needed a redo surgery. A laparoscopic exploration was performed. As a reason for dysphagia, a too tight posterior hiatoplasty was diagnosed, which was managed laparoscopically. No abnormality with the wrap was observed. After this remedial operation, the patient became symptom free. The annually performed symptom assessments revealed no recurrence of any of the three major reflux symptoms, and no further case of dysphagia was observed during the average of 56 months follow-up.

Discussion

The etiology and pathophysiology of hypertensive lower esophageal sphincter are still unknown. It is thought to be a primary esophageal motility disorder characterized by elevated LES pressure and predominant symptoms of dysphagia and chest pain.[7–9] A recent study from Gockel et al. [10] showed that typical reflux symptoms also frequently present in patients with HLES. They found a 75% of regurgitation and 71% of heartburn beside the 71% of dysphagia and 49% chest pain in HLES patients. Furthermore, 26% of the patients who also underwent 24-h esophageal pH monitoring in this series presented with abnormal esophageal acid exposure. In our study, all patients had primary symptom of reflux and abnormal DeMeester score on 24-h esophageal pH monitoring, which is due to our patient selection. The reason for this selection was the hypothesis that abnormal esophageal acid reflux can cause an elevation in the pressure of LES to "protect" the esophagus mucosa from further acidic injury. This reaction of a sphincter muscle to acid is not an undescribed phenomenon. Reports on the association of GERD and Zenker diverticula with elevated upper esophageal sphincter pressure have been published.[11,12] In some reports, even the connection between gastroesophageal reflux disease and achalasia was also suspected.[13–15] Furthermore, Sullivan [16] reported that after small intravenous doses of pentagastrin increased the LES pressure in all of eight patients with epigastric pain, which was believed to be due to a HLES. Unfortunately, surgical myotomy of these patients was unsuccessful. To investigate the hypothesis that GERD plays an important role of pathogenesis of HLES in a selected group of patients, a laparoscopic antireflux operation was performed. Criteria for selection were primary symptoms of GERD and HLES. Here, we have to mention that none of these six patients had severe dysphagia nor chest pain. The treatment of HLES, whether it is associated with reflux symptoms or with dysphagia and chest pain, is still controversial. Because HLES believed to represent an outflow obstruction medical therapy has been limited to muscle relaxant such as calcium channel blockers or nitroglycerine with little clinical efficacy.[17,18] Another possible treatment unfortunately with also similar disappointing result is the endoscopic management with dilatation or with botulinum toxin injection.[19,20] Surgical therapy for outflow obstruction would be a cardiomyotomy. Before the study, we have performed a laparoscopic cardiomyotomy with a Dor fundoplication in a patient with GERD associated HLES. Reflux control was insufficient in this case, the patients had to be reoperated, and a total fundoplication had to be performed. On the other hand, Champion et al. [21] found that in 16 patients with HLES, esophagomyotomy with posterior partial fundoplication provides good result regarding to dysphagia or chest pain. During our study period, four classic hypertensive LES patients were also observed with dysphagia and chest pain. They are all on medical therapy, and all underwent endoscopic pneumatic dilatations. One patient who did not respond to conservative therapy had laparoscopic myotomy and anterior fundoplication. Accepting the possibility that HLES may have more than one etiology and HLES can be secondary to gastroesophageal reflux, antireflux therapy seems to be the choice of treatment. Katzka et al. [22] reported nine patients with HLES and GERD who were treated successfully with antireflux medication and further three with fundoplication. Similar to all of our GERD patients, all six patients with HLES were on PPI before the operation. They all had temporary or partial relief of their reflux symptoms, and therefore, we were not able to use the PPI test as a guide for which hypertensive LES patient might respond to fundoplication. We also found, similar to the study from Barreca [23], that after a laparoscopic fundoplication, patients were symptom-free, preoperative dysphagia resolved, and no new-onset dysphagia appeared. In accordance to our results, Tamhamkar et al. [24] showed that after a Nissen fundoplication in 12 patients with GERD-associated HLES, all patients had complete relief of their dysphagia and chest pain. In addition, in this series, four further patients with isolated HLES was successfully treated with myotomy and partial fundoplication. Unfortunately, results were based only on symptoms and patients satisfaction, and no functional testing was performed. In our series postoperative 24-h esoph-

ageal pH monitoring and esophageal manometry was also performed. At a mean of 56 months follow-up, esophageal acid exposure and LES pressure were in a normal range, which is significantly different compared to the preoperative data. We found that by performing a 360° fundoplication, no new-onset dysphagia developed. Although a 60 Ch Bougie is inserted through the esophagus during the fundoplication, we do not believe that the bougie prevented early dysphagia in patients with HLES because we use the same technique for routine antireflux operations for GERD and still we observe approximately 10% of early temporary dysphagia 6 weeks after the operation. Instead, the originally high pressure of LES returned to a normal level. The latter finding seems to contradict the consideration that these HLES patients with GERD represent only GERD patients above the 95 percentile because normally, a fundoplication would elevate the pressure of LES as it was designed to do so. A possible explanation of our findings is that some HLES is caused by acid reflux and this elevated pressure can be interpreted as a protective action of LES to hinder gastroesophageal reflux. By eliminating excessive esophageal acid exposure with a fundoplication, the protective reaction of LES is no longer needed, and the pressure of LES can return to a normal level.

Conclusion

On the basis of our results, we must assume that there are two types of HLES. One is a primary esophageal motor disorder with symptoms of dysphagia and chest pain and with good response to myotomy. The other is the HLES, which is probably secondary to abnormal gastroesophageal acid exposure. In these patients, primary symptoms include typical symptoms of gastroesophageal reflux, and abnormal esophageal acid exposure can be observed on pH monitoring. Therefore, we suggest that in this subgroup of HLES patients, a 360° fundoplication should be performed instead of a cardiomyotomy, to control reflux and thereby eliminate the cause of HLES.

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Long-term Follow-up After Organ-Preserving Pancreatic Head Resection in Patients with Chronic Pancreatitis

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Abstract In chronic pancreatitis (CP), enlargement of the pancreatic head develops as a result of inflammatory alterations. This report relates to the results attained with an organ-preserving pancreatic head resection (OPPHR) in 135 patients in a 7-year period. The surgical procedure consists of a wide excision of the inflammatory tumor in the region of the pancreatic head, without division and cutting of the pancreas over the portal vein. Reconstruction, with drainage of the secretion from the remaining pancreas into the intestinal tract, takes place through a jejunal Roux-en-Y loop. Only one reoperation was required in consequence to anastomosis bleeding, but no mortality occurred in the postoperative period. The duration of hospitalization ranged between 7 and 12 days. The mean follow-up period was 4.1 years (range, 0.5–7.0). The late mortality rate was 3.7%. The quality of life, measured during the follow-up by using EORTC Quality-of-Life Questionnaire, improved in 89% of the patients. One hundred sixteen patients became complaint-free, while 14 patients had moderate symptoms; the weight increased by a median of 11.3 kg (range, 4–28). The 7-year experience clearly reveals that this OPPHR technique is a safe and effective procedure for definitive control of the complications of CP.

Keywords Chronic pancreatitis · Organ preservation · Pancreatic head resection · Long-term follow-up · Quality of life

Introduction

Patients with chronic pancreatitis (CP) characterized by severe pain pose a therapeutic challenge. In nearly one-third of these patients, enlargement of the head of the pancreas develops in consequence to inflammatory alterations, which leads to complications such as obstruction of the pancreatic duct, common bile duct stenosis, and duodenal compression. These are all indications for surgical treatment: resection of the pancreatic head, which is considered to be the pacemaker of the disease in CP.[1,2] The surgical treatment consists of different types of pancreatic head resection,[3] i.e., pylorus-preserving pancreaticoduodenectomy (PPPD),[4] Beger's duodenum-preserving pancreatic head resection (DPPHR),[5] the Bern modification of Beger's resection,[6,7] and Frey's longitudinal pancreaticojejunostomy combined with local pancreatic head excision (LPJ-LPHE).[8] In our surgical practice, mainly PPPD has been applied, but since 1999, in accordance with the modern organ-preserving concept, a safe procedure for organ-preserving pancreatic head resection (OPPHR) has been applied. The preliminary clinical results and follow-up achieved with this operation were published recently,[9,10] and in a prospective, randomized, control trial OPPHR was compared with PPPD to define the advantages of each operation with regard to the operation data, the postoperative complications, the induction of diabetes mellitus, the postoperative pain, and the quality of life (QoL) up to 1 year after operation. The prospective trial clearly confirmed that the two procedures are equally safe and effective with regard to pain relief, but OPPHR is superior to PPPD not only in the operative data and morbidity, but also in the QoL 1 year postoperatively.[11] This article reports on the late follow-up [average 4.1 years (range, 0.5–7.0)] results attained with our OPPHR in 135 patients.

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Material and Methods

Since February 1999, an OPPHR procedure has been performed in 135 patients [103 men and 32 women; mean age, 49.5 years (range, 28–63)] after the development of an inflammatory tumor of the pancreatic head [median diameter, 68 mm (range, 46 to 129 mm), as assessed by helical computed tomography (CT) scan. The preoperative morbidity involved frequent, sometimes severe abdominal pain, a significant loss in body weight in all patients, jaundice in ten patients, and latent and insulin-dependent diabetes mellitus (IDDM) in 16 and 21 patients, respectively. The mean interval between the appearance of the symptoms and the surgical intervention was 7.8±2.2 years. The etiology was connected with chronic alcohol ingestion in 86% (117 patients), the CP was associated with biliary stone disease in 14 patients (10%), and it was unknown in 4 patients. The diagnosis was confirmed by endoscopic retrograde cholangiopancreatograms (ERCP), sonography, and the CT scan. ERCP revealed that the diameter of the main pancreatic duct varied between 3 and 9 mm. In the 10 icteric patients and in 15 patients without jaundice, the common bile duct was stenotic, due to inflammatory tumor compression with prestenotic dilatation, combined with high levels of alkaline phosphatase (1,035±152 U/l). The CT scan demonstrated parenchymal calcification in 72 patients; 21 patients had pseudocystic cavities, and in 4 of them, a pseudocyst caused a subacute inflammation in the pancreatic head. No patient exhibited portal hypertension or superior mesenteric vein thrombosis.

Before the operation, prophylactic antibiotic (ceftriaxone) was used, and in the early postoperative period, all of the patients were treated by standard supportive treatment, consisting of total parenteral nutrition for 4 days, a proton pump antagonist (pantoprazole), suppression of TNF synthesis (pentoxifylline), and octreotide medication.[12] The oral nutrition was started on postoperative day 5.

Pancreatic functions were checked by means of stool elastase determination with a sandwich enzyme-linked immunosorbent assay (ELISA) method (Pancreatic Elastase1®, ScheBo Biotech, Giessen, Germany).[13] The glucose tolerance test was applied to check the endocrine function. Blood glucose levels were measured after 0, 30, 60, 90, and 120 min by means of a glucose oxidase assay after the administration of 75 g oral glucose.

Operative Procedure

The surgical procedure involved a wide local resection of the inflammatory tumor in the region of the pancreatic head and decompression of the organ and the intrapancreatic segment of the common bile duct if the prepapillary duct had become stenotic. The operative procedure started with the Kocher maneuver, partial dissection of the gastrocolic ligament for mobilization, and exploration of the head of the pancreas, without division and cutting of the pancreas over the portal vein. An intraoperative frozen section was performed for all patients; none of them revealed signs of malignancy. The following step of the operative procedure was ligation of the pancreaticoduodenal artery and the veins directed to the duodenum and to the superior mesenteric vein. The enlarged pancreatic head was excised in almost its entirety, leaving behind a bridge of pancreatic tissue about 10 mm wide, while a rim of pancreas (5 to 10 mm) remained beside the duodenum and on the upper margin of the pancreatic head. This wide excision gives a possibility for drainage of the pancreatic juice from the distal pancreas and for opening of the prepapillary obstructed common bile duct in the icteric patients and in patients with a stenotic common bile duct. The prestenotic dilated common bile duct was opened with an incision about 8–10 mm long, and the opened duct wall was sutured to the surrounding pancreatic tissue with interrupted Vicryl® 3/0 sutures. After careful hemostasis of the operative region, the reconstruction, with drainage of the secretion from the remaining pancreas into the intestinal tract, took place through a jejunal Roux-en-Y loop, with application of one-layer interrupted Vicryl® 2/0 sutures.[9] There was no indication or necessity for blood transfusion during the operation. The mean operating time was 165 min (range, 120 to 210 min).

Quality of Life

The quality of life (QoL) and pain score before and after surgery were assessed by using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30).[14] The EORTC QLQ-C30 has been reevaluated and demonstrated to be a valid and reliable tool to measure the QoL in patients with benign disease such as CP.[15] The EORTC QLQ-C30 comprises items relating to the physical status, the working ability, the emotional, cognitive, and social functioning, and an overall QoL scale. Pain intensity was estimated by means of a pain scoring system including a visual analog scale, the frequency of pain attacks, the use of analgesic medication, and duration of the inability to work. The overall pain score was given by the sum of the individual values divided by 4. This questionnaire was prospectively assessed at two time points during the study: before the surgical procedure and in the follow-up period (a mean of 4.1 years) after the operation.

Statistical Analysis

Statistical significance was estimated by using Student's *t* test or the Wilcoxon rank test, as appropriate. The level of

Table 1 Preoperative and Follow-up Pain Scores (n=105)

Criterion	Preoperative Score [median (range)]	Follow-up Score [median (range)]
Pain visual analog scale	82 (55–100)	10 (0–15)
Frequency of pain attack	75 (50–100)	12.5 (0–15)
Pain medication	20 (20–100)	0 (0–100)
Inability to work	75 (75–100)	0 (0–100)
Pain score	63 (50–100)	5.6 (0–37.5) (P<0.001)[a]

[a] Preoperative values were compared with follow-up values by the Wilcoxon rank sum test

significance was set at P<0.05. The results on the parametric data are expressed as means ± SD. Nonparametric data are expressed as medians.

Results

In 135 patients, the OPPHR procedure was performed after the development of an inflammatory tumor of the pancreatic head. In the postoperative period, only one reoperation was required in consequence of anastomosis bleeding, another case was treated conservatively, and one patient had pneumonia, but no septic complication, anastomosis insufficiency, or other problems; the morbidity was therefore 2.9%. There was no mortality in the postoperative period. In the 25 icteric and common bile duct stenotic patients, the liver functions normalized [serum bilirubin <22 μmol/l and alkaline phosphatase 332±92 U/l; compared with the preoperative data, the reduction was significant (P<0.05)] after the operation. The duration of hospitalization ranged between 7 and 12 days, with a median of 8.5 days. The histological examinations confirmed fibrosis and calcification in 63 and 72 patients, respectively.

The mean follow-up period was 4.1 years (range, 0.5 to 7.0). Five patients were lost to follow-up (3.7%). Complete follow-up data on 130 patients were included in the evaluation; the follow-up rate was therefore 96.3%. One hundred sixteen patients became complaint-free (89%), 14 patients had moderate symptoms, and the body weight increased by a mean of 11.3 kg (range, 4–28) (P<0.05). Within 2 years after operations, five patients were reoperated: a bilio-digestive bypass was performed in consequence of developed bile duct stenosis. In the follow-up period, a further six patients were admitted to the clinic with an acute episode of pancreatitis; all of them were treated conservatively. Readmission was therefore necessary in 11 of the 130 patients (8.4%). The late mortality was 3.7% (five patients); the reason was cardiovascular failure or an accident in four and one patient, respectively.

The stool elastase level increased slightly, but not significantly (from 124.3±33 to 132±39 μg/g; NS). The preoperative and postoperative endocrine functions remained in almost the same stage: 95 patients were normoglycemic, 6 had latent DM, and 20 had IDDM, but 9 patients with latent DM became IDDM (6.6%).

Both before the operation and during the follow-up, the patients were asked to complete the QoL questionnaire (EORTC QLQ-C30). A full answer was obtained from 105 patients (78%). The questionnaire was compared at two time points: (1) before the operation and (2) at a mean follow-up of 4.1 years (0.5–7) after the operation. The median pain score decreased by 91% (P<0.001) after surgery. No patient suffered a frequent pain attack, and only 10% of the patients mentioned moderate pain occasionally without any pain killer medication (Table 1). During the follow-up, the median global QoL improved by 100%. Apart from the cognitive functioning, the physical status, working ability, emotional and social functioning all improved significantly (P<0.05). The results of the symptom scales are summarized in Table 2.

Table 2 Preoperative and Follow-up Functioning Scale Scores (n=105)

Functioning Scale	Preoperative Score [median (range)]	Follow-up Score [median (range)]
Physical status	60 (20–100)	70 (20–100) (P<0.05)[a]
Working ability	50 (0–100)	70 (0–100) (P<0.05)[a]
Cognitive	50 (40–80)	66.7 (40–100) NS[a]
Emotional	25 (0–75)	66.7 (40–100) (P<0.05)[a]
Social	16.7 (0–66.7)	66.7 (0–100) (P<0.05)[a]
Overall quality of life	28.5 (14.3–57.1)	57.7 (33.3–100) (P<0.05)[a]

NS Not significant
[a] Preoperative values were compared with follow-up values by the Wilcoxon rank sum test

Discussion

Enlargement of the pancreatic head due to chronic inflammation causes permanent pain, obstruction of the pancreatic duct alone or together with the common bile duct, and duodenal compression. With these complications, surgical treatment is generally indicated. The aims of surgical therapy, therefore, are not only to eliminate pain, to manage the CP-associated complications of the adjacent organs, and possibly to preserve the endocrine and exocrine functions, but also (more importantly) to improve the patients' overall QoL and physical status, and also to provide for their social and occupational rehabilitation.[16] The objective outcome assessment of surgical treatment was made with the EORTC QLQ-C30, which has previously been demonstrated to be a valid and reliable tool with which to measure the QoL in patients suffering from benign diseases such as CP.[15,17]

In the past, classical Whipple's pancreatoduodenectomy (PD) and PPPD were applied as standard surgical procedures for pancreatic head complications in CP, but the long-term results and QoL after these operations were disappointing, with high rates of late morbidity and mortality.[18] Although two recently published articles have described better results,[19,20] it is generally accepted that these operations, involving the removal of healthy adjacent organs, do not seem to be warranted in this benign disease,[21] unless there is a strong suspicion of cancer.[22] In the past 20 years, these operations have generally changed, with the introduction of Beger's DPPHR[5] and Frey's LPJ-LPHE[8] procedure. In both, the resection or excision of the pancreatic head is limited, but achieves reliable pain relief and allows definitive management of the pancreatitis-associated complications of the adjacent organs and an improved QoL.[23–25] In the last 10 years, some important randomized studies have compared the different types of pancreatic head resection. Büchler demonstrated better pain relief and pancreatic function when DPPHR was compared with PPPD.[26] Almost the same results were reported by Klempa, who compared DPPHR vs PD: the degree of pain relief was equal, but the recovery was quicker, and the pancreatic function became better after Beger's operation.[27] Two randomized studies were also performed to analyze the pancreatic function and QoL after Frey's LPJ-LPHE or DPPHR: the level of pain relief was equal, but the QoL was better after Frey's operation.[28,29] Recently published articles based on the long-term follow-up of randomized trials have concluded that there was no difference with regard to the mortality, QoL, pain, or exocrine or endocrine insufficiency between the two operations and also indicated that these operations are advantageous for the treatment of CP. The decision as to which procedure to choose should be based on the surgeon's experience.[30,31]

In approximately 30% of patients with CP, the disease is primarily located in the head of the pancreas, which is known to act as the "pacemaker" to trigger the inflammatory process; resection of this inflammatory mass must be regarded as pivotal in the surgical intervention.[1,2,32] Basically, CP is a benign, but sometimes progressive disease, and the organ-preserving concept must therefore be accepted. The concept for our pancreatic head resection followed this directive, and our preliminary clinical results confirmed it.[9–11] The resection process removes only a sufficient part of the pancreatic head to guarantee the normal flow of both ductal systems (the bile and the pancreas) and to preserve the physiological gastroduodenal function.

This article is concerned with the late follow-up [on average, 4.1 years (range, 0.5–7.0)] results attained with our OPPHR on 135 patients. Our data demonstrated that OPPHR is a safe operative procedure, confirmed by the low morbidity (2.9%) and the absence of mortality among the patients in the postoperative period. An additional important feature is that the median duration of hospitalization was only 8.5 days. In the mean follow-up period of 4.1 years (range, 0.5 to 7.0), 116 patients became complaint-free (89%), while 14 had moderate symptoms, and the body weight increased significantly by a mean of 11.3 kg (range, 4–28). Readmission was required for 11 of the 130 patients (8.4%) as a consequence of relaparotomy (bilio-digestive bypass) or conservatively treated pancreatitis. The late mortality was 3.7% (five patients died). The preoperative and postoperative endocrine function remained in almost the same stage.

Pain relief and improvement of the QoL after surgery for CP in the patients were assessed by using the EORTC QLQ-C30. The completed questionnaires before and after the surgical treatment were evaluated in 105 patients (78%). Other patients were not included in the study because of incomplete data, or the lack of cooperation, or the data on the patients were not available. The median pain score decreased by 91% ($P<0.001$) after surgery. No patient suffered frequent pain attacks, and only 10% of the patients mentioned moderate pain occasionally. During the follow-up, the median global QoL improved by 100%. Apart from the cognitive functioning, the physical status, working ability, and emotional and social functioning all improved significantly ($P<0.05$).

On the basis of the early and long-term results of our OPPHR operations, the advantage of this procedure is the wide scale of possible indications, involving different pathologic processes, e.g., a subacute or chronic inflammation mass with a pseudocyst, ductal stenosis, or obstruction (common bile duct, pancreatic duct) caused by CP, small duct CP and some benign endocrine tumors localized in the pancreatic head.[33]

Conclusions

The results of this study clearly demonstrate that this OPPHR technique is a safe and effective procedure for definitive control of the complications after the inflammatory alterations of CP, and it is suggested that this operation is one of the best options for the management of patients with CP requiring surgery.

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Sentinel Bleeding After Pancreaticoduodenectomy: A Disregarded Sign

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Abstract
Introduction Delayed massive hemorrhage induced by pancreatic fistula after pancreaticoduodenectomy is a rare but life-threatening complication. The purpose of this study was to analyze the clinical course of patients with late hemorrhage, with or without sentinel bleeding, to better define treatment options in the future.
Material and Methods From April 1998 to December 2006, 189 pancreaticoduodenectomies were performed. Eleven patients, including two patients referred from other hospitals, were treated with delayed massive hemorrhage occurring 5 days or more after pancreaticoduodenectomy. Sentinel bleeding was defined as minor blood loss via surgical drains or the gastrointestinal tract with an asymptomatic interval until development of hemorrhagic shock. The clinical data of patients with bleeding episodes were analyzed retrospectively.
Results Eight of the 11 patients had sentinel bleeding, and seven of them had it at least 6 h before acute deterioration. Seven out of 11 patients died, five out of eight with sentinel bleeding. No differences could be detected between patients with or without sentinel bleeding before delayed massive hemorrhage. The only difference found was that non-surviving patients were significantly older than surviving patients. Delayed massive hemorrhage is a common cause of death after pancreaticoduodenostomy complicated by pancreatic fistula formation. The observation of sentinel bleeding should lead to emergency angiography and dependent from the result to emergency relaparotomy to increase the likelihood of survival.

Keywords Pancreas resection · Pancreatic fistula · Sentinel bleeding · Late bleeding · Delayed massive hemorrhage

Introduction

Pancreaticoduodenectomy (PD) is the only potentially curative treatment for patients with pancreas head carcinoma or with distal bile duct cancer. Although the operative mortality of PD has recently fallen to acceptable levels,[1,2] morbidity remains high.[3,4] Mortality is due most frequently to complications arising from the pancreato-enteric anastomosis.[5] A wide range of 11–45% incidence of pancreatic fistula has been reported due to variable definitions.[3,6–9]

Once an anastomotic leakage occurs, the associated morbidity rate can be as high as 40%.[6,10] The two most feared complications are abdominal sepsis and delayed massive hemorrhage (DMH). More than 10% of patients with anastomotic insufficiencies develop bleeding complications after PD.[11,12] Early postoperative bleeding is mostly due to technical failure, poor primary hemostasis, or insufficient management of coagulation disorders. DMH occurs in up to 5.8% of patients.[13,14] In most cases, it is caused by erosive bleeding of skeletonized vessels or rupture of pseudoaneurysms. The term "sentinel bleeding" was first introduced by Brodsky and Turnbull[15] in 1991 to describe the occasional observation that delayed massive bleeding after pancreaticoduodenectomy is sometimes preceded by a minor blood loss via surgical drains or the GI tract. The incidence and clinical impact of sentinel

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bleeding after PD are still not well defined. In this paper, we report a retrospective consecutive case series with delayed massive hemorrhage after PD. The aim of this report is assessment of the role of sentinel bleeding in patients with DMH after pancreaticoduodenctomy. This paper will also propose possible therapeutic strategies, which should be evaluated for their impact on mortality.

Material and Methods

A retrospective chart review was carried out for all consecutive patients who were treated in our hospital with PD between April 1998 and December 2006 (n=189). Nine patients with delayed massive hemorrhage after PD were identified. The digital archives of discharge letters and OR notes from the same time span were searched, and two further patients were identified, who were referred to our department with insufficiencies of the pancreatico-jejunostomy and who developed DMH while being treated in our hospital.

DMH was defined as a potentially life-threatening bleeding leading to hemorrhagic shock with the need for blood transfusions, occurring five or more days after PD in patients who had been hemodynamically stable until then. Sentinel bleeding was defined as minor blood loss via surgical drains or the GI tract with an asymptomatic interval between blood loss and development of hemorrhagic shock. Pancreatic leak was defined as drain fluid with an amylase level three or more times higher than the blood level after the third postoperative day.[16]

The records of all patients with DMH were then analyzed in detail for the patient's sociodemographic and clinical characteristics, for sentinel bleeding, for the presence of pancreatic fistula, and for diagnostic and therapeutic interventions related to the bleeding. Furthermore, the extent of hemodynamic instability, the duration of hemorrhagic shock, the number of blood units transfused, the duration of postoperative ICU treatment, and the outcomes were extracted from the patient files.

Student's t test was used to compare patients with vs without sentinel bleeding and to compare survivors vs non-survivors of DMH. The comparisons aimed to obtain additional information about the possible risk factors.

Operation Technique

The pancreaticoduodenectomy was performed with distal gastrectomy as standard Kausch Whipple procedure in 121 patients. Pylorus preservation was performed in 68 patients. Reconstruction of the alimentary continuity using two independent jejunal loops was performed in 104 instances. All anastomosis were performed by end-to-side technique. A standard lymphadenectomy is routinely performed, including skeletonization of the hepatic artery from the hepatic pedicle to the celiac axis and removal of the interaortocaval lymph nodes on the right of the superior mesenteric artery. The stump of the gastroduodenal artery is left around 5 mm long and is closed with a suture ligature. Prophylactic octreotide was routinely administered with 6 mg/day for 5 days. All patients were postoperatively admitted to our surgical intensive care unit.

Results

A total of 11 patients (six men) with DMH after PD were treated during the observation period, with a median age of 62 years (range 51–72 years). Late hemorrhage after PD occurred in 9 of 189 patients (4.7%). Hemorrhage after pancreatic fistula formation occurred in 8 of 28 patients (28.6%). Of the 28 patients detected with a pancreatic fistula, five patients (17.8%) had a grade A leak, 11 patients (39.3%) had a grade B leak, and 12 patients (42.9%) had a grade C leakage according to the ISGPF definition.[16]

The patient characteristics, treatments, and outcomes of patients with DMH are presented in Tables 1 and 2.

Only one of the 11 patients did not have a pancreatic fistula. According to the ISGPF definition, nine patients had a grade C leak, and one patient a grade B leakage.[16] A pancreatic fistula was clinically evident in seven patients and was initially treated conservatively in four patients. Operative revision was performed in three of these seven patients, with one total pancreatectomy and two reanastomosis and extensive drainage. Two insufficiencies of the pancreaticoduodenostomy were diagnosed during reoperation due to severe late bleeding, and one more was found during autopsy. The mortality of patients with late hemorrhage was 63% (7 out of 11 patients). Origins of bleeding were the common hepatic artery (n=2), the gastro-/duodenojejunostomy (n=2), the gastroduodenal artery (n=1), the celiac trunk (n=1), and the postal vein (n=1). In two cases, bleeding site was the splenic artery, in one patient after total pancreatectomy and in one patient referred from another hospital. In two patients, origin of bleeding remained unclear.

Patients With vs Without Sentinel Bleeding

No differences were found between patients with vs without SB before DMH. Eight out of 11 patients had SB, seven of them at least 6 h before hemorrhagic shock developed. Five of the patients with SB had hematemesis, one with melena, 17–47 days after pancreatectomy. These patients underwent endoscopy up to three times before

reoperation. During endoscopy, three out of five patients had a massive deterioration and went into hemorrhagic shock. Only one out of five patients undergoing endoscopy could be treated endoscopically. Three SBs occurred via the drainage at postoperative days 6 and 8. Five out of eight patients with SB died due to consequences of massive bleeding and ongoing sepsis (Table 2).

Three patients had no sentinel bleeding. One patient died in acute hemorrhagic shock without preliminary signs of bleeding or insufficiency of the pancreaticojejunostomy. The insufficiency was diagnosed only at the autopsy, which revealed the portal vein as the origin of bleeding. One patient with acute bleeding and shock was immediately operated upon, and the eroded hepatic artery was reconstructed. The postoperative course was prolonged but then uneventful. One other patient with an early insufficiency of the pancreaticojejunostomy was operated upon five times, including completion pancreatectomy on the third postoperative day after PD. He died 65 days later from acute intraabdominal bleeding (Table 1).

Survivors vs Non-Survivors of DMH

There was a statistical significant difference in age between surviving and non-surviving patients (56.5 years survivors vs 66.3 years non-survivors).

No differences could be found between survivors and non-survivors for the period of time between diagnosis of the pancreatic fistula and PD, the prevalence of sentinel bleeding or not, or the origin of bleeding.

There was a trend for the period between SB and shock to be shorter in surviving patients ($p=0.073$).

Discussion

Postoperative bleeding complications are reported in 5–16% of patients after PD and are associated with a high morbidity and mortality.[1,3,17–20] In cases of pancreaticointestinal anastomosis leakage, the occurrence of postoperative hemorrhage is associated with a mortality rate of 15–58%.[18,19,21–23] In these cases, bleeding can occur as hematemesis or melena and thus mimic intraluminal bleeding. Some authors differentiate between early/late bleeding and erosive arterial bleeding.[24] Early postoperative bleeding occurs within the first 24 h and can be distinguished from late bleeding which occurs, in most cases, in the second or third week after the operation.[8] Patients with early bleeding were not analyzed in this study.

Late bleeding after PD is usually massive with peripheral circulatory impairment. It occurs suddenly beyond the second or third postoperative weeks in hemodynamically stable patients, sometimes after an apparently uneventful

Table 1 Delayed Massive Hemorrhage After Pancreaticoduodenectomy: Bleeding Episodes And Treatment

Pat.	Diagnosis of Pancreatic Fistula on Postop. Day	Initial Presentation of Bleeding	Bleeding at Postop. Day	Sentinel Bleeding	Interval SB/ Shock/Hours	Origin of Bleeding	Treatment	Outcome
1	6	Drainage	14	No	0	Common hepatic artery	Suture ligature, bypass hepatic artery, pancreatectomy	Survived
2	5	Drainage	65	No	0	Splenic artery	Resuscitation	Death
3	Postmortem	Hematemesis	9	No	0	Portal vein	Resuscitation	Death
4	5	Hematemesis	20	Yes	No shock	Duodeno-jejunostomy	Endoscopic treatment	Survived
5	No fistula	Drainage	6	Yes	6	?	Lavage	Survived
6	7	Hematemesis	20	Yes	12	Splenic artery	3 Endoscopies suture ligature	Death
7	5	Drainage	8	yes	24	?	Erythroconcentrates	Death
8	19 Intraop.	Hematemesis Melena	19	Yes	6/30	Celiac trunc	Endoscopy Suture ligature	Death
9	10	Hematemesis	47	Yes	6	Gastro-jejunostomy	Endoscopy pancreatectomy, removal GJ	Death
10	8	Hematemesis	17	Yes	48	Common hepatic artery	Endoscopy 2 days preop. suture ligature Pancreatectomy	Death
11	7 Intraop.	Drainage	7	Yes	1.5	Gastroduodenal artery	Suture ligature	Survived

Table 2 Delayed Massive Hemorrhage After Pancreaticoduodenectomy: Patient Characteristics

	Surviving	Not surviving	SB	No SB	All
	N=4	*N*=7	*N*=8	*N*=3	*N*=11
Age	51–61(56.3)	53–72 (66.3) P=0.034	53–72 (63.2)	51 /61/72 (61.3)n.s	51–72 (62.63)
Sex					
Female	1	4	4	1	5
Male	3	3	4	2	6
Diagnosis					
Chronic pancreatitis		1		1	1
Pancreas head CA	3	6	8	1	9
Cancer distal common	1			1	1
Bile duct					
UICC Stage					
II	2	1	2		2
III	1	5	5	1	6
IV	1	1	1	1	2
ICU Stay (days)	2.75 (±2.36)	19.29 (±28.6)	Median 2	Median 6	1–65
Hospital Stay	37.7 (± 9.5)	30.571 (± 23.2)	30.12 (± 15.47)	41.3 (± 28.9)	9–65
Number of Reoperations	1, 1, 1, 2	1, 0, 4, 1, 5, 1, 0	1, 0, 1, 1, 1, 5, 1, 1	2, 4	
Number of Transfusions	4 (±1.6)	4.28 (±2.69)	4 (±1.512)	4.67 (±4.16)	4.2 (±2.3)
Operative Reconstruction					
Single loop	2	4	4	2	6
Double loop	2	3	4	1	5
Known Pancreatic Fistula/Insufficiency	3	5	6	2	8
Sepsis	1	5	5	1	6

postoperative course. The incidence of DMH in our patients was low and comparable to the literature. The majority of patients with such a late bleeding in this series as well as in the literature are characterized by an initial "sentinel bleeding", heralding the onset of the more sinister gastrointestinal or intraabdominal bleeding by 6 h to 10 days.[15,17–19] Several studies have focused on this particular type of postoperative complication detailing the incidence, the diagnostic and therapeutic strategy, and the patient's outcome.[1,3,6,15,17–19,25–30] Santoro et al.[30] combined the literature and found late bleeding in 67 of 2,389 cases (2.7%). A pancreatic leak, an intraabdominal abscess, or other abdominal septic complications were reported to be associated in 85% of cases. The overall mortality rate was 40%, and emergency exploration was required in a mean of 80% of cases.

Risk factors for DMH published in the literature uniformly are clinically evident signs of local or systemic sepsis. Other risk factors have been identified, such as insufficiency of the hepaticojejunostomy, male sex, and a longer duration of jaundice.[24] None of these factors could be affirmed in this study probably due to the small number of patients. In the clinically stable patients, precious time was lost with endoscopy or observative treatment. Although it is described in the literature, "sentinel bleeding" still is an underestimated sign. There is a short window of time to improve the patient's chance of survival, but, unfortunately, this time is often lost or wasted.

De Castro et al.[14] reported four patients with sentinel bleeding without DMH from 388 patients with PD. De Castro et al. showed that none of these four patients had septic complications in the postoperative course. In our series, all (n=8) patients with sentinel bleeding also developed DMH. Three patients with only intraoperatively or postmortem diagnosed insufficiencies of the pancreaticojejunostomy did not have clinical signs of sepsis or pancreatic fistula formation.

Patients with pancreatic fistula formation or insufficiency of the pancreatic anastomosis should usually undergo early reoperation if signs of sepsis occur. But pancreatic fistula can also be treated conservatively (15/28 of our patients) if no local or systemic inflammatory reaction occurs. In these cases, strict surveillance of abdominal drains and weekly angio-CT scan should be performed to detect the development of pseudoaneurysm of the main retroperitoneal vessels.[30]

Recent case reports and studies have shown that angiography with transarterial embolization (TAE) seems to be a treatment option for preventing major hemorrhage if any anomaly is detected, but the clinical relevance has not yet been evaluated in larger enough studies. Sato et al.[27]

and Yoshida et al.[28] have both shown that transarterial embolization allows for temporary control of major hemorrhaging, with hemodynamic stabilization of most patients and a low recurrence rate (of about 14%). Nonetheless, in their series, it did not seem to be an alternative to exploration, given that the mortality rate was as high as 57% due to systemic sepsis and multi-organ failure. Transarterial embolization should at the least be able to achieve hemostasis and could help to get the patient out of hemorrhagic shock into a stable condition bridging time to operation. De Castro et al.[14] concluded that the surgical approach remains the most promising treatment of late intraabdominal hemorrhage, perhaps combined with intraoperative endoscopy. Van Berge et al.[19] showed that even in a surgical unit where TAE was generally accepted as a treatment option, surgical intervention was the treatment of choice. Transarterial embolizations of branches of the celiac trunk are performed very often in our radiological department (>100/year), especially for chemo-embolization of liver tumors, and TAE also has a place in treatment of bleeding or pseudoaneurysms. In this series of patients with DMH after pancreaticoduodenectomy, no TAE was performed. This was due to the fact that three patients had no sentinel bleeding and of the eight patients remaining, five had signs of gastrointestinal bleeding, which were misunderstood and led to endoscopy in four patient. From the recent published data, emergency angiography should be included in the algorithm of treatment of patients with sentinel bleeding after pancreaticoduodenectomy.

A very aggressive surgical approach including completion pancreatectomy is associated with a high mortality rate and should be indicated for uncontrolled pancreatic leakage before late intraabdominal bleeding occurs.[30] Encouraging results have also been reported after minor surgical procedures: proximal ligation of the hepatic or splenic artery, oversewing the pancreatic stump, occlusion of the pancreatic duct, or radiological interventions alone.[6,12,22,23,31–34] Comparing the clinical courses and records of the patients in this series, no common characteristics of the patients with late bleeding apart from the more or less clinically apparent fistula could be detected. This study is, like others, limited by the small number of patients and by its retrospective design, but it describes one of the largest samples of patients with DMH, with consideration of SB and its treatment options.

Conclusion

When sentinel bleeding occurs, an emergency angiography should be considered as an option either for definite treatment or at least for bridging time until the operation and for stabilizing the patient for the relaparotomy. If embolization fails, no further diagnostic procedures should be performed except for endoscopy in the operating room in individual cases.

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ORIGINAL ARTICLE

Metabolic Changes in the Pigliver During Warm Ischemia and Reperfusion Measured by Microdialysis

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Abstract
Aim Portal triad clamping can cause ischemia–reperfusion injury. The aim of the study was to monitor metabolic changes by microdialysis before, during, and after warm ischemia in the pigliver.
Material and Methods Eight pigs underwent laparotomy followed by ischemia by Pringle's maneuver. One microdialysis catheter was placed in each of four liver lobes. A reference catheter was placed in a muscle. Microdialysis samples were collected at intervals of 30 min starting 2 h before 1 h of total ischemia followed by 3 h of reperfusion. Glucose, lactate, pyruvate, and glycerol concentrations were measured. Blood samples were drawn for determination of alanine aminotransferase, alkaline phosphatase, and bilirubin together with total leukocytes and prothrombin time.
Results All parameters were stable during the baseline period. During the ischemic period, lactate levels increased significantly ($P<0.05$) followed by a rapid decrease after reperfusion. A transient increase was observed for glucose and glycerol. Pyruvate showed a slight increase from the time of ischemia. The lactate–pyruvate ratio increased rapidly after initiating ischemia and decreased immediately after reperfusion. A slight increase in transaminase levels was observed.
Conclusions During and after warm ischemia, there were profound metabolic changes in the pigliver observed with an increase in lactate, glucose, glycerol, and the lactate–pyruvate ratio. There were no differences between the four liver lobes, indicating the piglivers homogeneity.

Keywords Warm liver ischemia · Portal triad clamping · Reperfusion · Microdialysis · Metabolic changes

Introduction

Major operative blood loss and transfusions requirements have been related to increase morbidity, mortality, and recurrence after hepatectomy either for primary or secondary malignancies. Liver metastases from colorectal carcinoma are one of the leading causes for liver resections in the western society.[1–3] Having in mind that the liver receives about one quarter of the total cardiac output, different techniques are used to reduce intra-operative blood loss including portal triad clamping by the Pringle maneuver (PM). Portal triad clamping, however, causes ischemia and may result in ischemia–reperfusion (I/R) injury to the remaining liver, which, in turn, may result in liver failure.[4]

Microdialysis provides an opportunity for continuously monitoring metabolic changes in liver and other tissues.[5–8] A number of different metabolites can be measured to monitor hepatic metabolism. In particular, glucose, lactate, pyruvate, and glycerol have been used.[9]

The aim of the present study was to monitor metabolic changes in the pigliver during warm ischemia and the following reperfusion using monitoring of glucose, lactate, pyruvate, and glycerol with microdialysis and to compare these changes between the four liver lobes.

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Material and Methods

Eight female pigs (Danish Landrace/Yorkshire) with a body weight of approximately 60 kg (Påskehøjgård Centre, Aarhus, Denmark) were used for the experiments. The research procedure was conducted under a local project license (registration number: 2002-561-574) in accordance with the Danish regulations for animal experiments.

Animals were premedicated with an intramuscular injection of Midazolam 0.5 mg/kg, Azaperon 4 mg/kg, and Etomidate 0.5 mg/kg. After intubation, the animals were anesthetized with isoflurane gas (2–3%) and Fentanyl 0.05 mg/h, intravenously and mechanically ventilated in a respirator with 4 l of oxygen per minute and 4 l of N_2O per minute.

The left carotic artery and the left jugular vein were cannulated. Samples for blood gas analysis were drawn from the left carotic artery; blood pressure measurements were made in this vessel as well. Fluid and drugs were administered through the left jugular vein, and blood samples for measurements of alanine aminotransferase (ALT), alkaline phosphatase (AP), and bilirubin, together with total leukocytes and prothrombin time, were also drawn from this vessel. Finally, a urinary catheter was

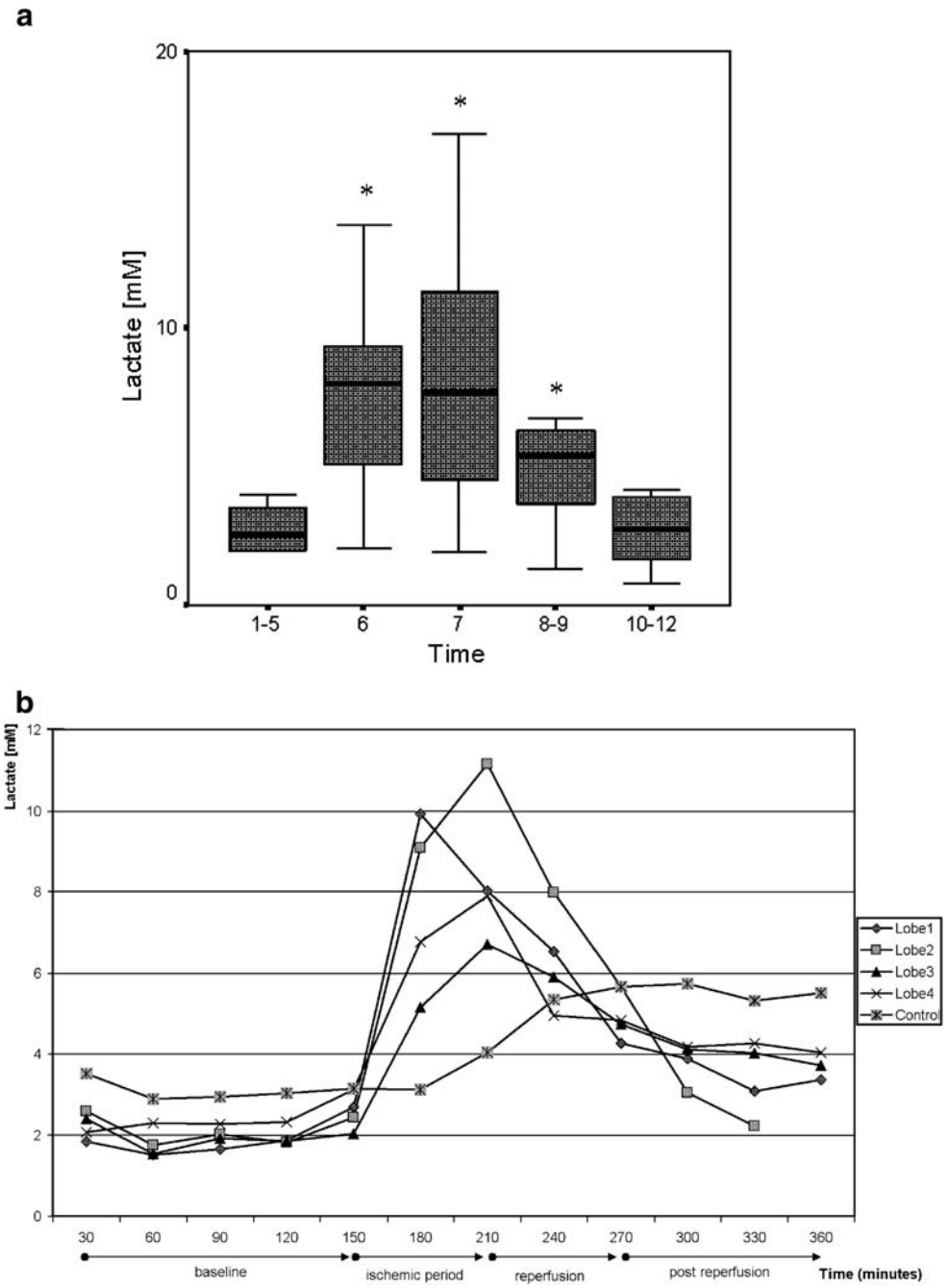

Figure 1 **a** Lactate levels in the whole liver as mean of the four lobes, at baseline (samples 1–5), during ischemia (samples 6, 7), reperfusion (sample 8–9), and post-reperfusion (10–12). *$P<$ 0.05 compared to baseline. **b** The dynamic in lactate levels in the four liver lobes and reference tissue during the four study periods, baseline (0–150 min), ischemia (150–210 min), reperfusion (210–270 min), and post-reperfusion (270–360 min). There was no significant difference between the four liver lobes.

placed, and rectal body temperature was measured and maintained at 37.0°C to 38.5°C. During the experiment, the pigs were administered a continuous infusion of Ringer's solution in doses of 4 to 6 ml kg^{-1} h^{-1}.

A midline laparotomy was performed. The liver was mobilized, and structures in the portal triad were exposed. Ischemia was performed using the portal triad clamping, i.e., the Pringle maneuver. One microdialysis catheter (CMA 60 Microdialysis Catheter, Stockholm, Sweden) was placed and fixed in each of four liver lobes. A reference catheter was inserted in the right psoas muscle. Catheters were connected to a microinfusions pump (CMA/106 Microinjection pump: CMA Microdialysis AB) and perfused with Ringers chloride at a flow rate of 0, 3 μl/min. After insertion of the probes a "washout period" of 1 h was used to flush the dialyses probes and to allow the liver tissue to recover from cellular damage due to the implantation procedure.

Microdialysis samples were collected at intervals of 30 min starting 2 h before 1 h of total ischemia (PM) followed by 3 h of reperfusion. All together, 12 samples were collected. In collected samples, glucose, lactate, pyruvate (reflecting carbohydrate metabolism), and glycerol (reflecting lipid breakdown through lipolysis or cell membrane disintegration) were analyzed using a CMA

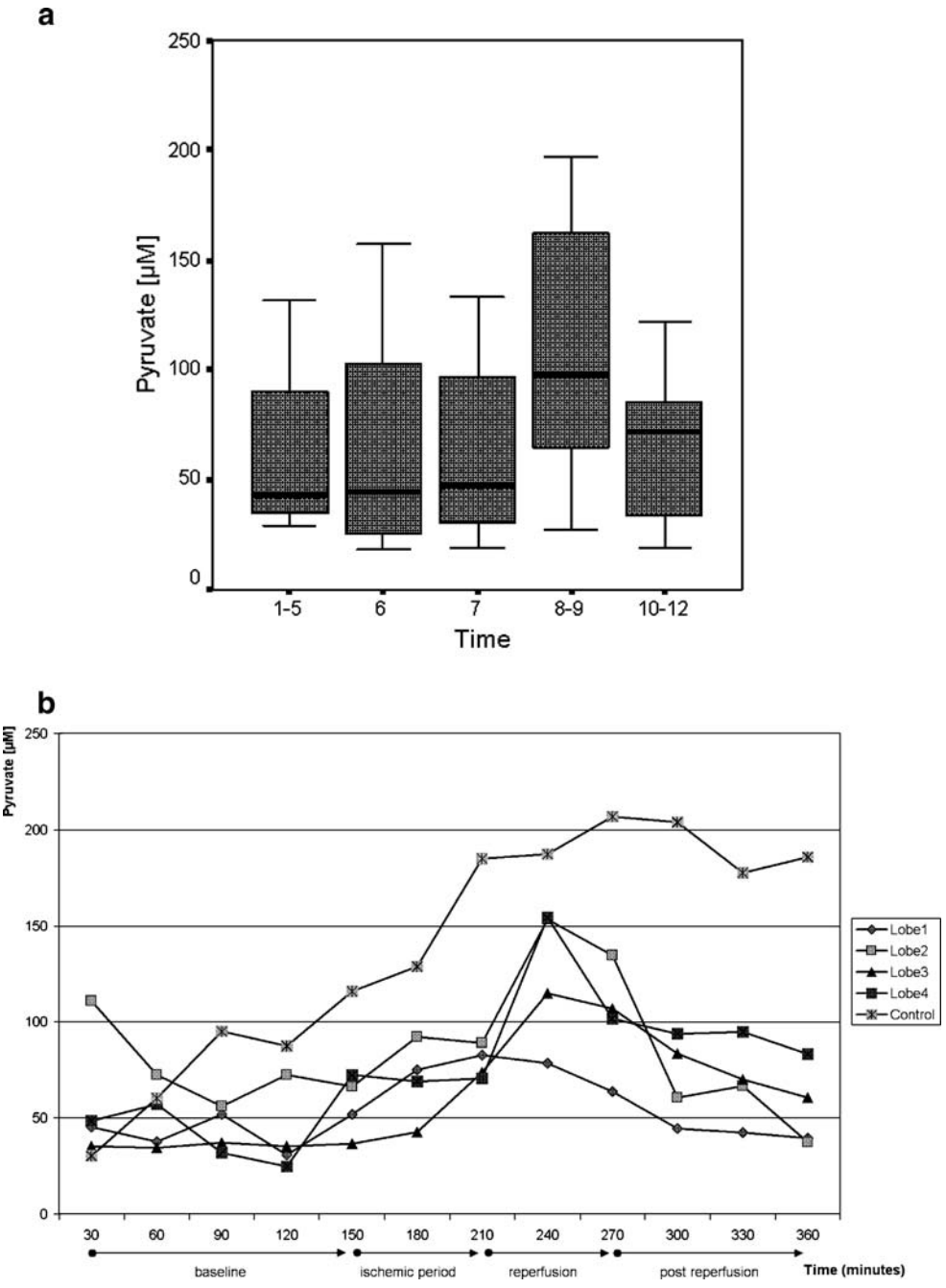

Figure 2 **a** Pyruvate levels in the whole liver as mean of the four lobes, at baseline (samples 1–5), during ischemia (samples 6, 7), reperfusion (sample 8–9), and post-reperfusion (10–12). **b** The dynamic in pyruvate levels in the four liver lobes and reference tissue during the four study periods, baseline (0–150 min), ischemia (150–210 min), reperfusion (210–270 min), and post-reperfusion (270–360 min). There was no significant difference between the four liver lobes.

600 microdialysis analyzer (CMA Micodialysis AB), and the lactate–pyruvate ratio (indicator of ischemia) was calculated. During the experiment, ALT, AP, and bilirubin, together with total leukocytes (TL) and prothrombin time (PT), were measured three times, at baseline, end of ischemia, and end of post-reperfusion.

Between events in the monitored tissue and collected dialysate, there was a time delay estimated to be approximately 30 min. Because of the time delay of 30 min, baseline was an average of time points 1 to 5. Time points 6 and 7 were an expression for the ischemic period. An average of time points 8 to 9 represents the reperfusion period, and an average of time points 10 to 12 represents the post-reperfusion period.

Statistical Methods

Statistical analyses were performed by SPSS® 10.0 programs (SPSS, Chicago, IL). The results are expressed as mean ± SEM. Comparisons of data within a group and between groups were performed by non-parametric Kruskal–

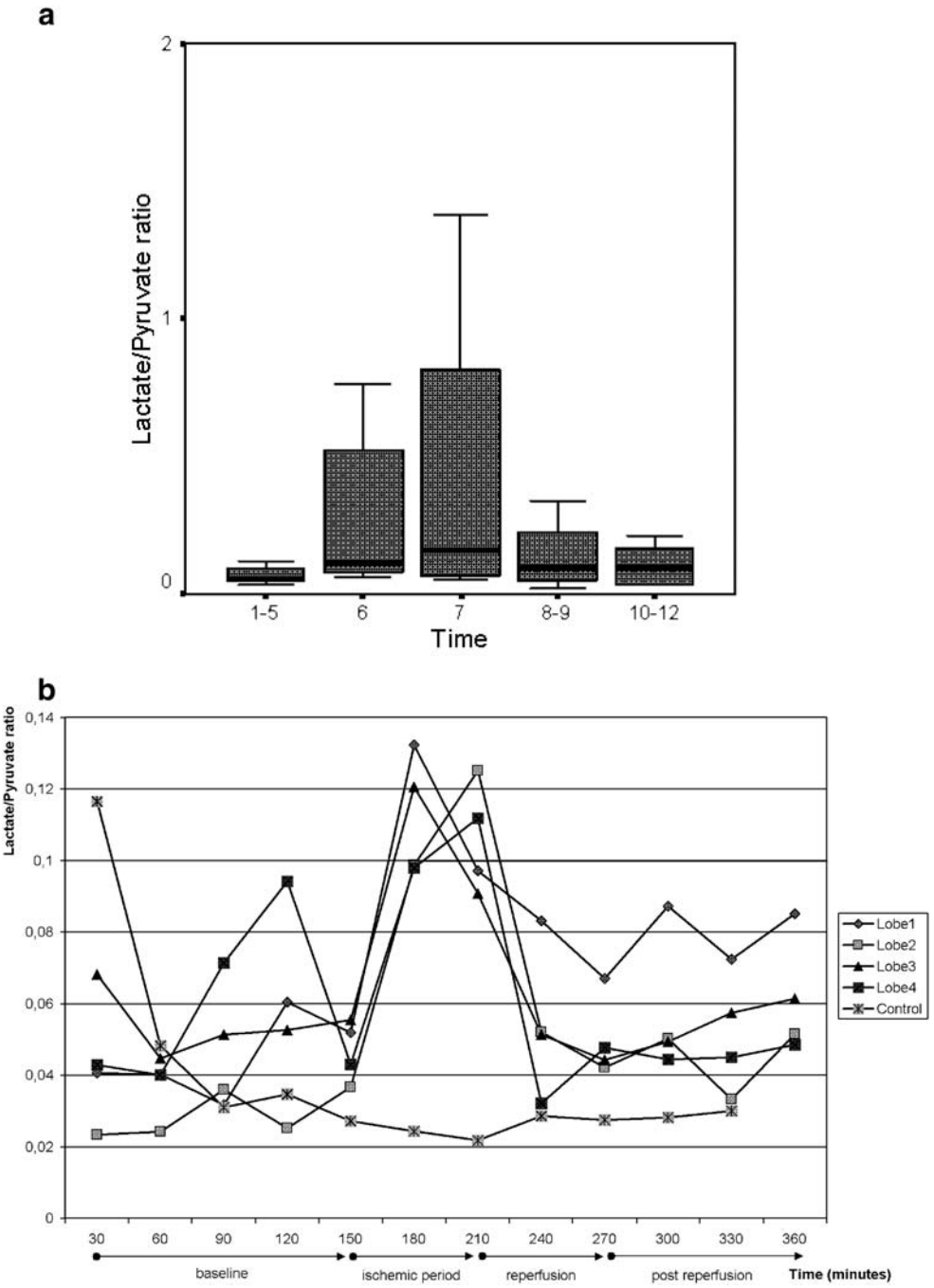

Figure 3 **a** Lactate–pyruavte ratio in the whole liver as mean of the four lobes, at baseline (samples 1–5), during ischemia (samples 6, 7), reperfusion (sample 8–9), and post-reperfusion (10–12). **b** The dynamic in lactate–pyruvate ratio in the four liver lobes and reference tissue during the four study periods, baseline (0–150 min), ischemia (150–210 min), reperfusion (210–270 min), and post-reperfusion (270–360 min). There was no significant difference between the four liver lobes.

Wallis test followed by the Mann–Whitney test. A P value< 0.05 was considered significant.

Results

Lactate

During the baseline period, lactate levels were stable (3±1 mmol/l). After start of total ischemia, lactate levels increased significantly ($P<0.05$) and continued to increase during the ischemic period. Lactate levels declined at start of reperfusion, but did not reach baseline (Fig. 1a). Lactate levels in the reference tissue remained stable during baseline and up to 30 min of ischemia. During the reperfusion period, lactate levels in the reference tissue showed a slight but insignificant increase.

There was no difference in lactate levels between the four lobes during the experiment (Fig. 1b).

Pyruvate

Pyruvate levels were stable during the baseline periods (62± 45 μmol/l). At the start of reperfusion, pyruvate started to increase. This continued until the time of post-reperfusion. From this time to the end of study, a decrease in pyruvate levels was

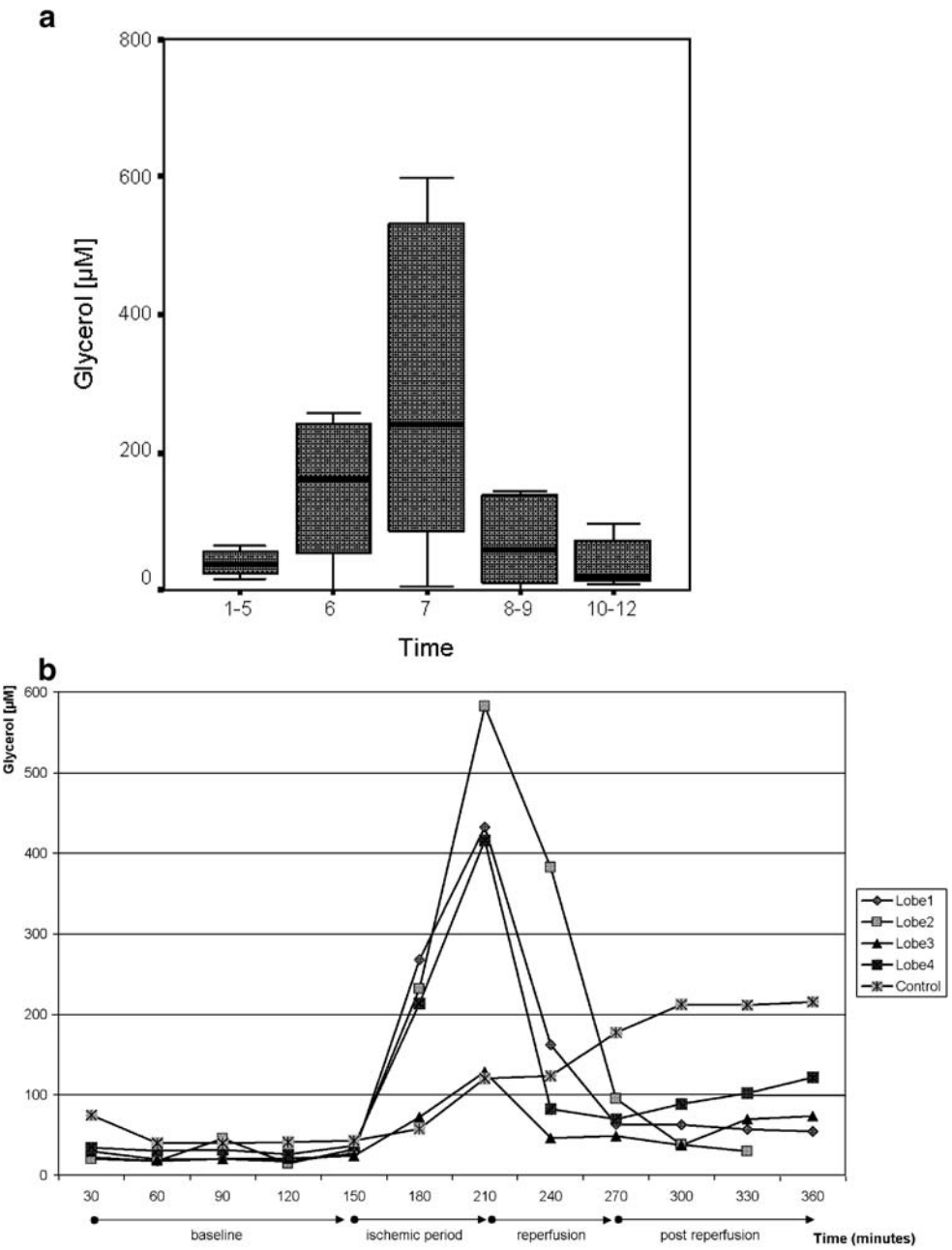

Figure 4 **a** Glycerol levels in the whole liver as mean of the four lobes, at baseline (samples 1–5), during ischemia (samples 6, 7), reperfusion (sample 8–9), and post-reperfusion (10–12). **b** The dynamic in glycerol levels in the four liver lobes and reference tissue during the four study periods, baseline (0–150 min), ischemia (150–210 min), reperfusion (210–270 min), and post-reperfusion (270–360 min). There was no significant difference between the four liver lobes.

observed (Fig. 2a). Pyruvate levels in the reference tissue began to increase at the start of the experiment, and this continued until half way of post-reperfusion (Fig. 2b). During the end of post-reperfusion, only minor alternations were observed.

There was no difference in pyruvate levels between the four lobes during the study period (Fig. 2b).

Lactate–Pyruvate Ratio

A low and stable lactate–pyruvate ratio was observed during the baseline period followed by a rapid increase in lactate–pyruvate ratio at start of the ischemic period. The lactate–pyruvate ratio decreased immediately at the start of reperfusion and returned to baseline levels before post-reperfusion (Fig. 3a). In the reference tissue, the lactate–pyruvate ratio showed a decrease in the beginning of the baseline period; hereafter, it remained stable for the rest of the experiment.

There was no difference in lactate–pyruvate ratios between the four liver lobes (Fig. 3b).

Glycerol

During the baseline period, glycerol levels remained stable (53±25 μmol/l). At the start of total ischemia, glycerol

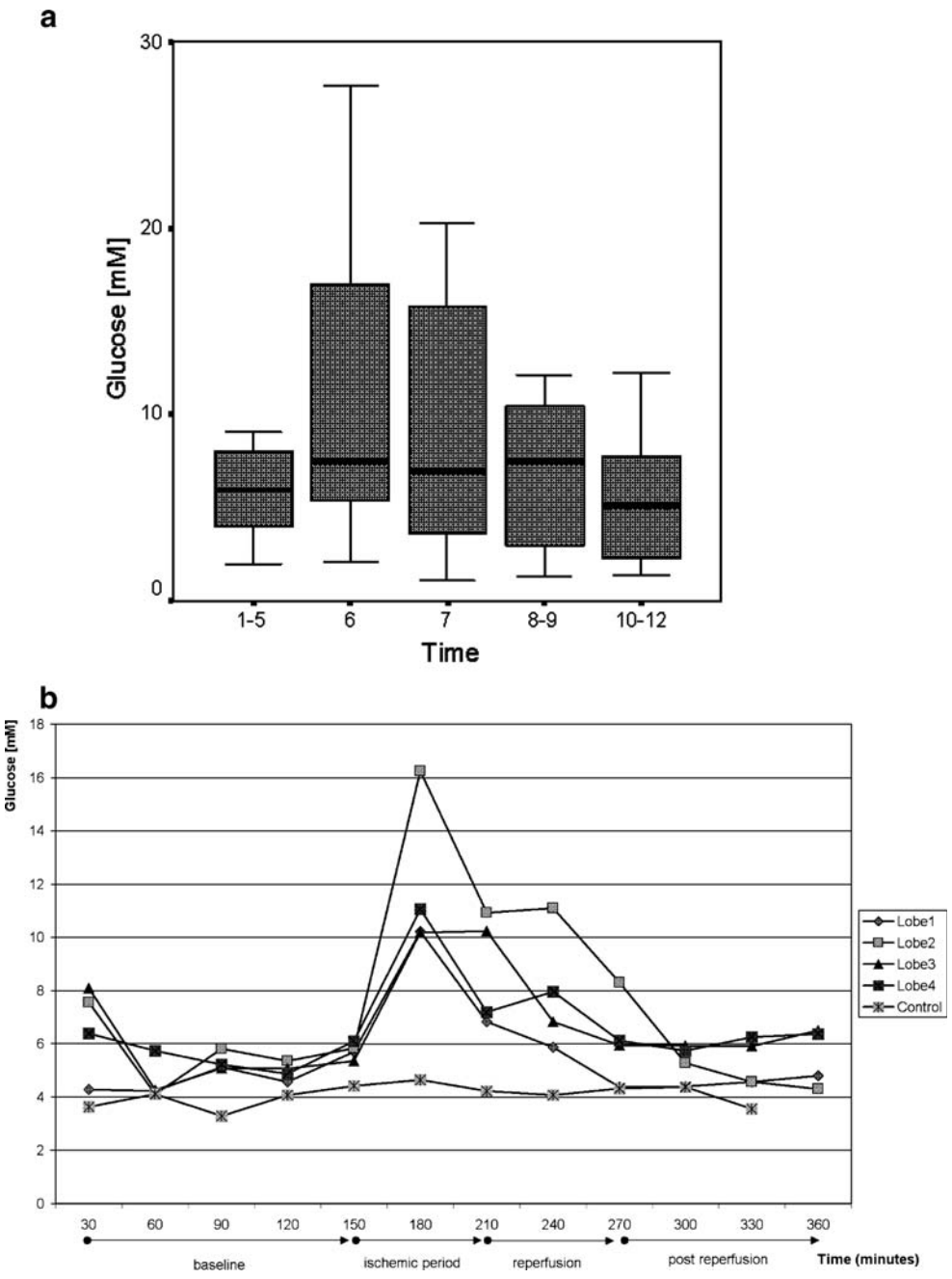

Figure 5 **a** Glucose levels in the whole liver as mean of the four lobes, at baseline (samples 1–5), during ischemia (samples 6, 7), reperfusion (sample 8–9), and post-reperfusion (10–12). **b** The dynamic in glucose levels in the four liver lobes and reference tissue during the three study periods, baseline (0–150 min), ischemia (150–210 min), reperfusion (210–270 min), and post-reperfusion (270–360 min). There was no significant difference between the four liver lobes.

levels increased rapidly and decreased as well rapidly from the time of start of reperfusion towards levels close to baseline and remained stable for the rest of the experiment (Fig. 4a). Glycerol levels in the reference tissue were stable until the end of the ischemic period; hereafter, a slight increase was observed.

There was no difference in glycerol levels between the four lobes (Fig. 4b).

Glucose

Glucose levels remained stable during the baseline period (6±3mmol/l). Immediately after the start of total ischemia and lasting for approximately 30 min, an increase in glucose levels was seen. At the end of ischemia, glucose levels began to decrease, and this continued during the whole reperfusion period until baseline levels were reached (Fig. 5a). Variations in glucose levels in the reference tissue were insignificant during the whole of the experiment.

There was no difference in glucose levels between the four lobes during the experiment (Fig. 5b).

Transaminase Levels

Changes in ALT, AP, and bilirubin together with TL and PT were insignificant (Table 1).

Discussion

In the present study, we have demonstrated marked metabolic changes in the pigliver during 60 min of warm ischemia and the following reperfusion evaluated by continuous monitoring of glucose, lactate, pyruvate, and glycerol by microdialysis. There was no difference in metabolic parameters between the four liver lobes.

Different techniques have been used to reduce intraoperative bleeding during liver resection, including portal triad clamping by the Pringle maneuver. Portal triad clamping, however, causes I/R injury and is a potential cause of hepatic failure, which, in turn, may result in postoperative death.[10] Having the aforementioned considerations in mind, early detection and monitoring of biochemical changes in the liver during warm ischemia/reperfusion could turn out to be of great clinical importance. Microdialysis is a method that provides the opportunity to continuously monitor metabolic changes in tissues. We chose to monitor glucose, lactate, pyruvate, and glycerol because these molecules reflect oxygen supply as well as cell membrane damage.[11]

Using Pringles maneuver, complete arterial and portal inflow occlusion were obtained. We chose not to take biopsies for histological analysis because we were concerned that the consequent liver cell damage could influence the metabolites determined by microdialysis.

During tissue ischemia, a change from aerobic to anaerobic metabolism normally causes an increase in lactate levels and a decrease in pyruvate levels.[12] In accordance with the above mentioned and a study by Nowak et al. on cold liver ischemia, lactate levels in the present study increased significantly after start of total ischemia. Surprisingly, however, we observed an increase as well in pyruvate levels during ischemia, not a decrease, as expected or as shown by Nowak et al.[9] However, similar observations were reported in a study by Silva et al.,[13] although these observations were limited to the time shortly after reperfusion. This discrepancy cannot be explained by collateral blood flow through the ligaments in the present study, as ligament and vessels were divided to avoid this. Also, surprisingly, we observed an increase in pyruvate levels in the reference tissue during the whole of the experiment. This increase in pyruvate levels was also seen during liver ischemia, despite the fact that we observed a simultaneous increase in lactate levels during the same period.

The lactate–pyruvate ratio is a well-known marker of cell ischemia, indicating an inadequate supply of oxygen and glucose.[14] In the present study, as expected, we observed a significant increase in lactate–pyruvate ratio immediately after initiating ischemia. After the start of reperfusion, lactate/private ratio decreased to baseline levels during 1 h and remained stable for the rest of the experiment, indicating normalization of liver blood flow.

Besides being a product of lipolysis, glycerol is also an indicator of cell membrane disintegration.[15] The significant increase in glycerol levels we observed during ischemia could be explained by injuries to the cell membranes. Immediately after the start of reperfusion, we observed a rapid decrease in glycerol levels, which could be explained by termination of the ischemic insult and a washout effect.

In our study, glucose levels increased immediately after start of total ischemia. Similar results were reported by Nowak et al.[9] during cold liver perfusion. From previous

Table 1 Transaminase Levels

	Time 1 Baseline	Time 2 Ischemia	Time 3 Reperfusion
ALT (U/l)	53 (±15)	56 (±14)	67 (±20)
AP (U/l)	98 (±27)	117 (±45)	134 (±5)
Bilirubin (μmol/l)	3 (±2)	3 (±2)	3 (±2)
PT	0.96 (±0.09)	0.93 (±0.19)	0.84 (±0.18)
TL (10^9/l)	18.62 (±6.6)	19.78 (±8.88)	24.28 (±8.88)

Liver parameters: alanine aminotransferase (ALT), alkaline phosphates (AP), and bilirubin together with total leukocytes (TL) and prothrombin time (PT)

studies, it is known that glucose levels are affected by changes in glucose supply and uptake into the tissue.[16] In general, glucose levels indicate the amount of glucose available in the tissue as a reflection of plasma levels and local blood flow. During ischemia, reduced blood flow decreases the delivery of glucose to the liver. The increase in glucose concentration as observed in the present study could be explained by a release from injured hepatocytes.

The degree of increase in transaminase levels has, in several studies, been related to the degree of hepatic injury resulting from ischemia.[3,17,18] In the actual study, we observed only minor increases in transaminase levels, ALT, AP, and bilirubin together with TL and PT. This indicates that the hepatic injuries in the present study were minor or the time for follow-up during reperfusion was too short to see any cell damage. Despite the fact that the hepatic injuries caused by 1 h of warm ischemia and the following reperfusion seem to be minor, we demonstrated pronounced metabolic changes during the experiment. Microdialysis could therefore be of value for early detection and monitoring of changes in the liver during warm ischemia and the following reperfusion and may turn out to be of great clinical importance.

In conclusion, the results obtained from this study have given us an insight in metabolic changes in the pigliver during warm ischemia induced by PM and the following reperfusion. During and after warm ischemia, there were profound metabolic changes in lactate, pyruvate, glucose, and glycerol measured by microdialysis. There were no differences between the four liver lobes, indicating the piglivers homogeneity. In these circumstances, one catheter for microdialysis will be sufficient in future studies for monitoring metabolic changes in the whole of the liver during warm ischemia and reperfusion.

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Prognostic Factors and Recurrence of Small Hepatocellular Carcinoma after Hepatic Resection or Microwave Ablation: A Retrospective Study

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Abstract
Purpose This study aims to analyze the long-term therapeutic results of small HCC less than 5 cm in diameter after microwave ablation (MA) or hepatic resection (HR) and choose factors that could predict metastasis and recurrence of small HCC.
Materials and Methods The metastasis and recurrence of 194 patients with one HCC less than 5 cm in diameter who underwent curative HR or MA between January 1995 and December 2004 were reviewed retrospectively; immunohistochemistry was used to analyze the expressions of VEGF, bFGF, and c-Met in HCC tissues. Posttreatment prognostic factors were evaluated by multivariate analysis using Cox's proportional hazards model. The variables included the expressions of these three proteins in HCC tissues, the clinical and pathologic characteristics of the patients.
Results The retrospective study showed that 1-, 3-, and 5-year disease-free survival rates of patients with single HCC of diameter <5 cm were 71.3, 57.0 and 32.5%, respectively. Furthermore, 1-, 3-, and 5-year disease-free survival rates of the patients in MA group and resection group were 72.8, 54.0 and 33.0%; 68.5, 60.0, and 25.6%, respectively. There was no significant difference in disease-free survival rates between these two groups. The result of multivariate analysis showed that differentiation degree of HCC and the expressions of VEGF and c-Met in HCC tissues could be as the independent prognostic factors affecting metastasis and recurrence in patients with small HCC, whereas the methods of therapy had no impact on prognosis.
Conclusions The metastasis and recurrence rate after MA is similar to that after HR, and the methods of therapy do not affect the prognosis of small HCC. The metastasis and recurrence of patients with small HCC will differ depending on tumor differentiation, expressions of VEGF and c-Met in HCC tissues.

Keywords Small hepatocellular carcinoma (HCC) · Metastasis and recurrence · Microwave ablation (MW) · Hepatic resection (HR) · VEGF · c-Met

Introduction

With the development of modern imaging systems, such as ultrasonography, computed tomography, and magnetic resonance imaging, more and more small HCCs of diameter <5 cm can be detected and diagnosed early.

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Hepatic resection (HR) is still the first choice of treatment for a small HCC in patients with relatively good liver function, but it is possible only in a small proportion of patients because of impairment of liver function caused by underlying cirrhosis.[1–3]

Microwave ablation (MA), as a minimally invasive management technique, has been developed and improved greatly within the last several years. It has been widely used as an effective approach to small HCC in China due to the minimal damage to liver function, convenient manipulation, low complications, and mortality.[4] However, whether MA exerts an effect on metastasis and relapse of small HCC has not been determined yet.

Despite adequate patient selection, the 3-year disease recurrence rate may exceed 50%[5,6] after hepatic resection. Some of the recurrences may be metachronic tumors developed in the underlying cirrhotic liver, but the vast majority of

those neoplastic nests that arise during follow-up should be considered a consequence of tumor dissemination before surgery.[7] The recurrence risk is usually estimated by conventional pathological grading[8,9] that is a consequence of a molecular deregulation (such as gene deletion, etc.). Thus, molecular tumor profiling might offer a better risk estimation.

Tumor angiogenesis is an essential step for tumor growth and metastasis. Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and c-Met are documented to play a significant role for a development of neovasculature. VEGF selectively induces mitosis in the endothelial cell.[10] It was reported that serum VEGF in patients with lung cancer may serve as a useful indicator of tumor angiogenesis.[11] bFGF is also a potent stimulator of angiogenesis and metastasis, too.[12] c-Met is the product of oncogene c-met and the receptor of hepatic growth factor (HGF).[13] Nearly all the functions of HGF are realized through c-Met, and c-Met plays an important role in the development of recurrence and metastasis of tumors.[14] However, the potential roles of VEGF, bFGF, and c-Met in the recurrence and metastasis of small HCCs less than 5 cm in diameter, regardless of the treatment methods, remain unclear.

To our knowledge, no long-term results dealing with disease-free survival rate of single HCC less than 5 cm in diameter and their influencing factors in a large series of patients have been published up to date, and no detail comparisons have been done on the curative effect of HR and MA. However, many variables related to the characteristic of the tumor and the coexisting cirrhosis may greatly influence survival of patients with HCC after percutaneous ablation.[15] In this study, different factors—including clinicopathologic factors and methods of therapies—were observed, and their relationship to outcome was assessed to determine whether any of these factors might be used to predict the prognosis of HCC and to determine whether the methods of therapy would affect the disease-free survival.

Materials and Methods

Patients

From January 1995 to December 2004, there was a total of 122 patients, and 109 patients with a single HCC of diameter <5 cm accepted MA or HR, respectively. Because this was a respective study, some patients after HR or MA underwent recheck in their local hospitals, which resulted in the failing of following up. Therefore, 8 cases in MA group and 29 cases in HR group were failed to follow up. Then, 114 cases in MA group and 80 cases in HR group were included in our study. There were 99 men and 15 women aged 25–81 years (mean age ± SD, 54.82±11.44 years) in MA group, and the maximum diameter of the nodules ranged from 1.1 to 4.9 cm (mean ± SD, 2.9±1.4 cm). There were 72 men and 8 women aged 18–78 years (mean age ± SD, 57.66±14.31 years) in HR group, and the maximum diameter of the nodules ranged from 1.2 to 4.8 cm (mean ± SD, 3.0±1.3 cm).

Eligibility criteria of the patients of MA or HR group in our study were as follows: (1) single nodular HCC lesion of diameter <5 cm; (2) absence of portal vein thrombosis or extrahepatic metastases; the number of tumor nodules and absence of portal vein thrombosis were evaluated on the basis of ultrasound as well as computer tomography (CT) or magnetic resonance imaging (MR) results.

Histologic diagnosis of HCC was obtained for all the specimens after an ultrasound-guided biopsy or operation. The specimens were assessed blindly by two pathologists independently. The histologic grades of the tumor were defined as follows: well differentiated, corresponding to Edmondson's Grade I or I~II; moderately differentiated, corresponding to Edmondson's Grade II or II~III; or poorly differentiated, corresponding to Edmondson's Grade III or III~IV. Histologic grade was obtained in all patients.

None of the patients received antineoplastic treatment before treatment. All MA treatments were performed at our institution with approval from the institutional ethics committee. Written informed consent was obtained from every patient at enrollment.

Assessment of VEGF, bFGF and c-Met in HCC by Immunohistochemistry

Immunohistochemistry was done on both cancerous tissues and pericancerous tissues to see if VEGF, bFGF, and c-Met played important roles in the development of HCC. All the samples acquired from resection had pericancerous tissues. Then, both the cancerous tissues acquired from biopsy or resection and the pericancerous tissues acquired from resection were fixed by 10% formaldehyde, embedded in paraffin and made for serial microtome sections 4 μm in thickness. One section was stained with hematoxylin and erosin to be reviewed by a pathologist for reassurance. Three sections were used for immunohistochemistry and one section was used for negative control. Microtome sections were deparaffinized, hydrated, digested with 0.1% trypsin for 1 h at room temperature and treated with 3% hydrogen peroxide to quench endogenous peroxidase. Non-specific staining was blocked with 30% goat serum. The sections were subsequently treated with the primary antibody (Mouse antihuman VEGF, bFGF, and c-Met monoclonal antibodies). The concentrations of these three monoclonal antibodies were 1:50, 1:100 and 1:100, respectively. After the primary antibody incubation, two rinses in phosphate-buffered saline (PBS) for 3 min each

were performed, and the secondary antibody (Goat anti mouse IgG) was added to the sections for 20 min. Sections were then rinsed in PBS twice, and avidin–biotin–peroxidase complex was added on the sections for 30 min. After three rinses in PBS, the sections were incubated with diaminobenzidine (DAB) for 5 min and rinsed twice with distilled water. The sections were then placed into hematoxylin to counterstain for 1 min and washed in running water for 3 min. The sections were air dried, mounted with glycerol gelatin, coverslipped, and analyzed under the light microscope for positive staining. Positive staining was indicated by a prominent brownish pigmentation in the cytoplasm while the negative controls displayed no or few such signs.

A negative control was performed to ensure the specificity of immunostaining by using PBS as the first antibody.

Evaluation of Score

Both the extent and intensity of staining were considered when scoring VEGF, bFGF, and c-Met expression. The extent of positive staining was scored as follows: 0, ≤10%; 1, >10–25%; 2, >25–50%; 3, >50–75%; and 4, >75%. The intensity was scored as follows: 0, negative; 1+, weak; 2+, moderate; and 3+, strong. The final score was obtained by multiplying the extent scores and intensity scores, producing a range from 0 to 12. Scores 9–12 were defined as strong staining pattern (++), scores 0–4 were defined as negative expression (−), and scores 6–8 were defined as intermediate staining pattern (+). All the staining was evaluated by two independent observers.

Baseline Characteristics of the Patients and the Tumor Pathological Study

To ensure the comparison between HR group and MA group, baseline characteristics of the patients and tumor pathological characteristics (including gender, age, Child-Pugh classification, HBsAg/HCV positive rate, liver cirrhosis positive rate, tumor differentiation, AFP level, total bilirubin level, albumin level, VEGF positive rate, bFGF positive rate, and c-Met positive rate) were compared between MA group and HR group.

Microwave Coagulation System

A UMC-I (ultrasound-guided microwave coagulator-I) delivery system (PLA General Hospital and Institute 207 of the Aerospace Industry Company, Beijing, China) with a microwave frequency of 2,450 MHz and a power output range of 10–80 W was used. The system was equipped with a thermal monitoring module and a needle electrode (1.4 mm in diameter) with a Teflon coating to prevent tissue adhesion. A 14-gauge percutaneous microwave coagulation therapy guiding needle was used for puncture guidance. The temperatures in the treatment region could be monitored dynamically with iron-constant thermocouples, which were inserted and fixed into a 20-gauge needle sheath with naked tips of 0.5 cm to measure the temperature.

Microwave Ablation Technique

Therapeutic principle: Coagulation volume should extend 0.5 cm beyond the tumor's border. A single- or multiple-puncture and emission technique was used depending on the size of the tumors. For tumors less than 1.7 cm in diameter, the single-puncture and emission technique was used. For tumors larger than 1.7 cm, a multiple-puncture and simultaneous emission technique was required. Two electrodes were used for tumor of 1.7–3.0 cm with an interelectrode distance of 1.6–1.8 cm. For tumors larger than 3.0 cm, 3–4 overlapping ablations were needed. The maximum distance of 1.6–1.8 cm between two electrodes was set through computer simulation with a goal of maximizing the total coagulated area while simultaneously merging the two areas into one bigger area which attains an integrated shape, leaving no tumor tissue untreated. Pull-back technique was used in tumors larger than 4.0 cm. Tips of the electrodes were first positioned in the deepest part of the tumor, after the deep portion was coagulated, the electrodes were withdrawn approximately 1.5–2.0 cm to ablate the superficial portion of the tumor. According to this principle, a detailed protocol was worked out before treatment on an individual basis including the placement of the electrodes, power output setting, emission time, and appropriate approach.

After local anesthesia was induced, a 14-gauge guiding needle with a sheath was inserted and positioned at the designated place of the tumor under sonographic guidance, and then the stylet of the guide needle was pulled out. After the electrode was introduced through the sheath of the guide needle, the sheath was withdrawn approximately 4–5 cm while keeping the electrode needle at its place to ensure that a portion of at least 4 cm from the tip of the electrode was exposed. After electrode insertion, one to three thermocouple needles were introduced into the designated sites approximately 0.5 cm outside the tumor through an 18-gauge needle sheath under sonographic guidance. Before the energy application was started, a general anesthesia using a combination of propofol (Diprivan, Zeneca Pharmaceuticals, Wilmington, DE) and ketamine (Beijing Pharmaceuticals, Beijing, China) was administered via the peripheral vein. Given that the heat generated by the microwave could be carried away by the flowing blood. In tumors with feeding vessels defined on color Doppler sonography, electrode were placed at the region of the vessels and a high-energy setting (75 W for 100–300 s) was used to destroy them before the ablation procedure.

In general, an output setting of 60 W for 300 s was used during ablation. Radiation was stopped when the measured temperature at 0.5 cm outside the tumor reached 60°C or maintained a level of 54°C continuously for 1 min.

Disease-Free Survival Rate, Complications and Causes of Death

Disease-free survival rate, complications, and causes of death of 194 patients with HCC of diameter <5 cm after HR or MA was analyzed.

Table 1 Patients' Profiles

Variable	HR group (n=80)	MA group (n=114)	Total (n=194)	P value
Gender				
Male	72	99	171	0.503
Female	8	15	23	
Age (years)				
≤40	8	12	20	0.957
40–60	48	70	118	
>60	24	32	56	
Child-Pugh classification				
A	52	71	123	0.757
B	28	40	68	
C	0	3	3	
HbsAg/HCV				
(+)	71	98	169	0.569
(−)	9	16	25	
Liver cirrhosis				
Present	71	96	167	0.369
Absent	9	18	27	
Tumor differentiation				
Well	46	55	101	0.379
Moderate	20	31	51	
Poor	14	28	42	
Pre-treatment serum AFP (ng/ml)				
≤20	44	58	102	0.571
>20	36	56	92	
VEGF				
(+/++)	50	68	118	0.332
(−)	30	46	76	
bFGF				
(+/++)	48	80	128	0.141
(−)	32	34	66	
c-Met				
(+/++)	52	77	129	0.712
(−)	28	37	65	
Total bilirubin (μmol/l)				
≥21.0	27	47	74	0.291
<21.0	53	67	120	
Albumin (g/l)				
≥50	15	21	36	0.954
<50	65	93	158	

P<0.05 implied statistical significance

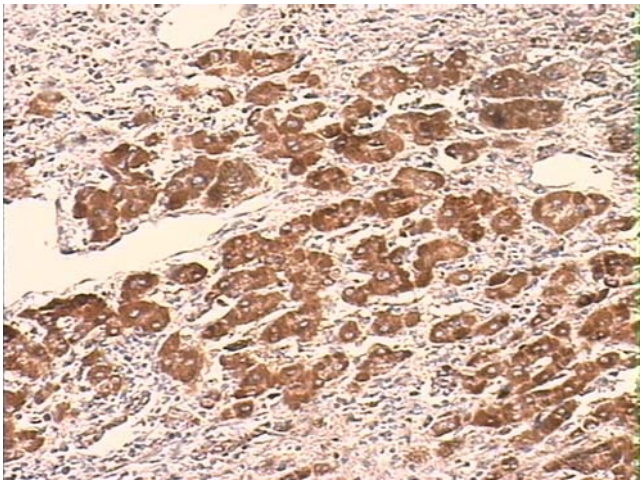

Figure 1 Expressions of VEGF in HCC. The color of positive cells is in *brown* (×400).

Prognostic Factors Analyzed

The prognostic factors analyzed included patient- and tumor-related variables and methods of therapy. Patient-related factors included gender (male or female); age (40 years of age or younger, 40–60 years old or older than age 60); degree of liver dysfunction (class A, B or C according to the classification of Child-Pugh); associated HBsAg or anti-HCV and liver cirrhosis (present or absent); total bilirubin (≥21.0μmol/l, or <21.0μmol/l); Albumin (≥50 g/l, or <50 g/l); tumor-related factors included tumor cell differentiation (well, moderately, or poorly); preoperative serum AFP level (<20 ng/ml or >20 ng/ml); expression of VEGF (strong, intermediate or negative); expression of bFGF (positive or negative); expression of c-met (positive or negative).

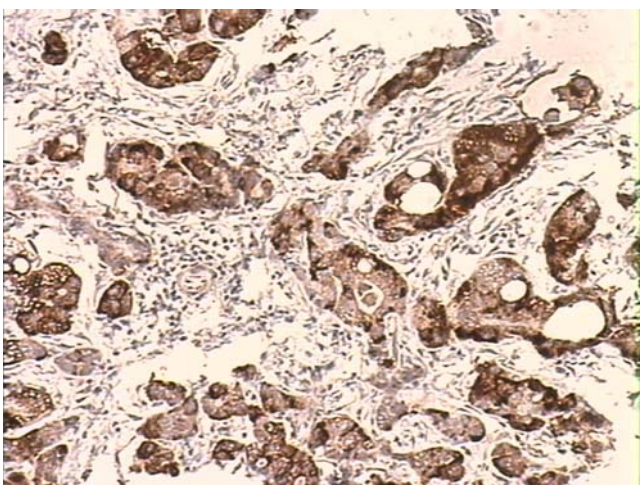

Figure 2 Expressions of c-Met in HCC. The color of positive cells is in *brown* (×400).

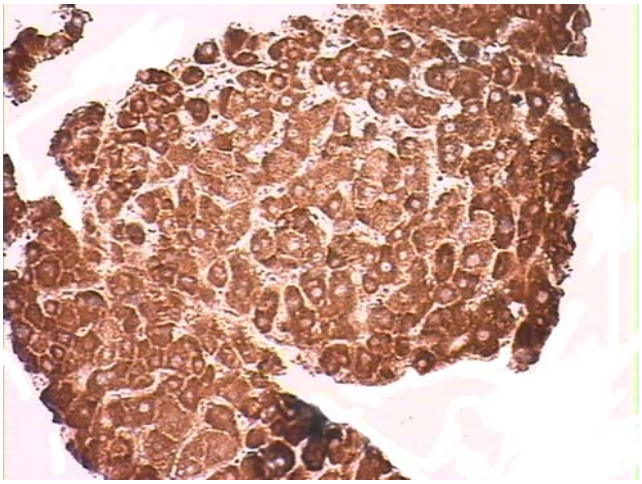

Figure 3 Expressions of bFGF in HCC. The color of positive cells is in *brown* (×400).

Follow-Up Protocol

The follow-up was calculated starting from the beginning of MA or HR. In patients dying without evidence of recurrence, their follow-up was censored at the time of death.

Statistical Analysis

Baseline data of the patients were reported as means ± SD. A comparison between groups was done using the χ^2 test. The univariate analysis to identify predictors of survival was performed by the Kaplan–Meier method and compared by the log rank test. Results in the univariate analysis were considered statistically significant if the probability of occurrence by chance was less than 0.05. Cox's proportional hazards model was used to determine those variables independently related to recurrence. Statistical analysis was done with SPSS package (SPSS, Chicago, IL). A p value less than 0.05 was considered to be statistically significant.

This was a retrospective study and it was approved from the institutional ethics committee.

Table 2 Expressions of VEGF, bFGF and c-Met in Cancerous Tissues and Pericancerous Tissues

	Cancerous tissues		Peri-cancerous tissues		*P* value
	Positive	Positive rate	Positive	positive rate	
VEGF	118	60.8%	11	13.8%	<0.05
bFGF	128	66.0%	12	15.0%	<0.05
c-Met	129	66.5%	10	12.5%	<0.05

Table 3 Comparison of VEGF, bFGF and c-Met in Cancerous Tissues Between HR Group and MA Group

	HR group		MA group		*P* value
	Positive	Positive rate	Positive	Positive rate	
VEGF	50	62.5%	68	59.6%	>0.05
BFGF	48	60.0%	80	70.2%	>0.05
c-Met	52	65.0%	77	67.5%	>0.05

Results

Baseline Characteristics of the Patients and the Tumor Pathological Study

As we can see in Table 1, there was no significant differentiation between MA and HR groups in gender, age, Child-Pugh classification, HBsAg/HCV positive rate, liver cirrhosis positive rate, tumor differentiation, AFP level, total bilirubin level, albumin level, VEGF positive rate, bFGF positive rate, and c-Met positive rate. Then the disease-free survival rates of both groups could be compared.

Expressions of VEGF, bFGF and c-Met

VEGF, bFGF and c-Met were all expressed in the cytoplasm with prominent brownish pigmentation (see Figs. 1, 2, 3). The expressions of VEGF, bFGF and c-Met in the cancerous tissues were 60.8%, 66.0%, and 66.5%, respectively. The expressions of VEGF, bFGF and c-Met in the pericancerous tissues were 13.8%, 15.0%, and 12.5%, respectively. The expressions of VEGF, bFGF, and c-Met in the cancerous tissues were all significantly higher than

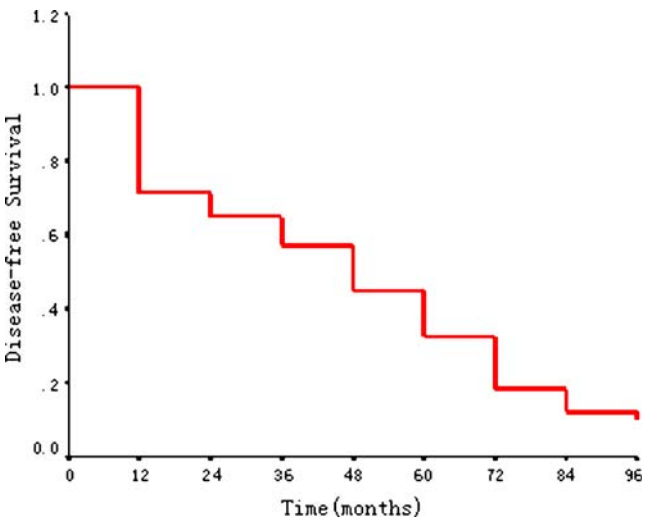

Figure 4 Disease-free survival rate of 194 patients with small hepatocellular carcinoma after HR or MA. The 1-, 3- and 5-year disease-free survival rates are 71.3, 57.0, and 32.5%, respectively.

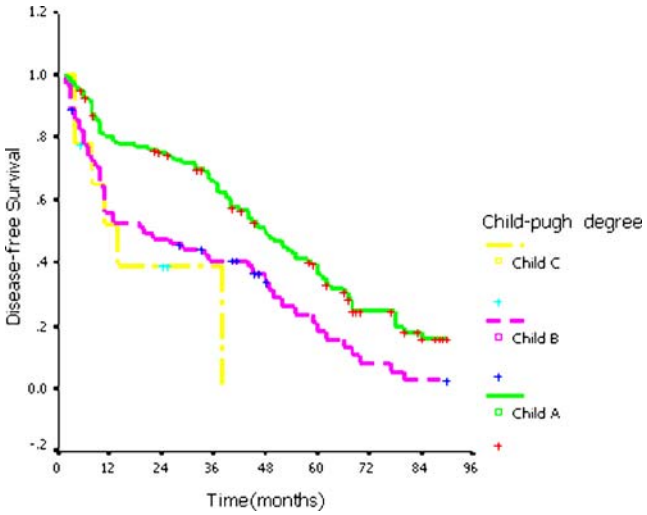

Figure 5 Disease-free survival of patients with HCC according to Child-Pugh classification. The survival in patients of Child A (green line) was significantly longer than that of Child B (red line) and Child C (yellow line). And the survival in patients of Child B (red line) was significantly longer than that of Child C (yellow line) (P=0.000).

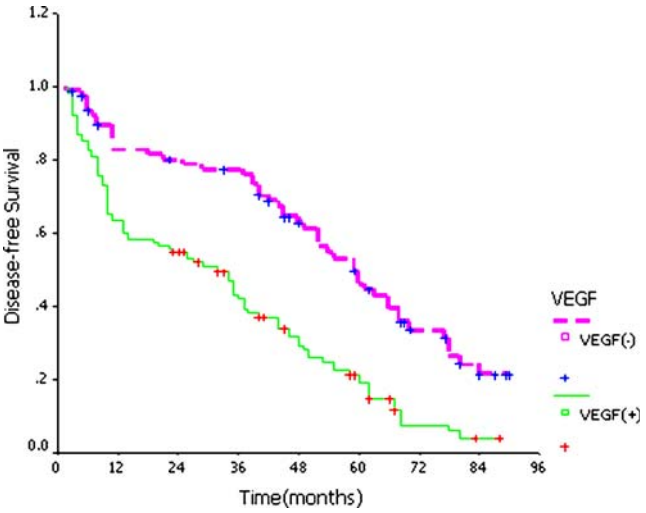

Figure 7 Disease-free survival of patients with HCC according to VEGF tumor vs. non-tumor (VEGF T/NT) expression by immunohistochemistry. The disease-free survival was significantly lower in patients with expression of VEGF compared with patients without expression (P=0.000).

those in pericancerous tissues (see Table 2). The expressions of VEGF, bFGF, and c-Met in the cancerous tissues of HR group were 62.5, 60.0, and 65.0%, respectively. The expressions of VEGF, bFGF, and c-Met in the cancerous tissues of MA group were 59.6, 70.2, and 67.5%, respectively. There were no significant differentiations in the expressions of VEGF, bFGF, and c-Met between MA group and HR group (see Table 3).

Disease-Free Survival Rate and Causes of Death

The 1-, 3-, and 5-year disease-free survival rates of all the patients with single HCC of diameter <5 cm were 71.3, 57.0, and 32.5%, respectively (Fig. 4). The 1-, 3-, and 5-year disease-free survival rates in MA group were 72.8, 54.0, 33.0%, respectively. The 1-, 3-, and 5-year disease-free survival rates in HR group were 68.5, 60.0, 25.6, respectively. There was no significant difference in the disease-free survival rates between HR group and MA group.

In MA group, recurrence or new tumors was observed in 80 patients (70.2%) during the follow up period. Fifteen patients (13.2%) had local regrowth of a microwave-treated lesion. New tumors in the same Couinaud segment but apart from the original sites occurred in 26 cases (22.8%). New tumors were found in different Couinaud segment of the liver in 27 cases (23.7%), while extrahepatically in 12

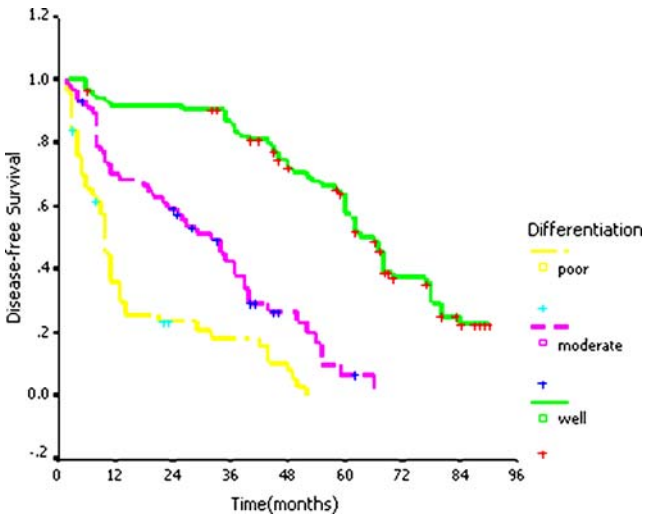

Figure 6 Disease-free survival of patients with HCC according to tumor differentiations. The differences in survival rates among patients with HCCs of different degrees were statistically significant (P=0.000).

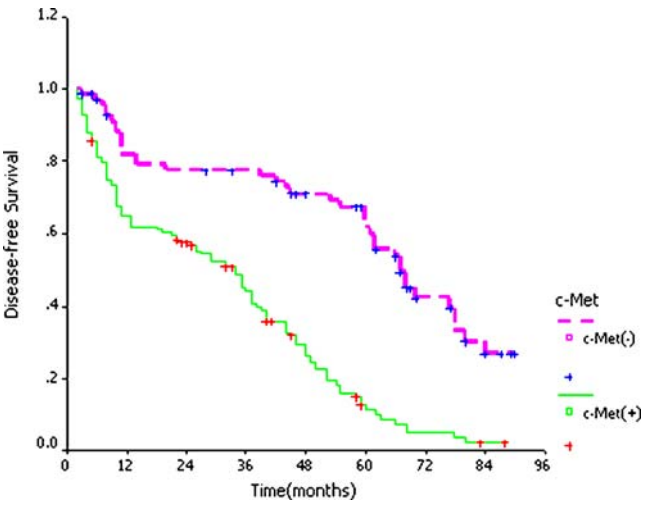

Figure 8 Disease-free survival of patients with HCC according to c-met tumor vs. non-tumor (c-met T/NT) expression by immunohistochemistry. The disease-free survival was significantly lower in patients with expression of c-Met compared with patients without expression (P=0.000).

cases (10.5%). In HR group, recurrence or new tumors were observed in 61 patients (76.3%) during the follow up period. New tumors in the ipsilateral lobe but apart from the resection line occurred in 17 cases (21.3%). New tumors in the contralateral lobe and apart from the resection line occurred in 26 cases (32.5%). New tumors near the resection line occurred in eight cases (10.0%). Extrahepatic new tumors were found in ten cases (12.5%).

Table 4 List of Variables Examined at Univariate Analysis

Variable	Patients	1-year disease free survival (%)	3-year disease free survival (%)	5-year disease free survival (%)	Median survival time	95% confidence interval	Significance (log-rank test)
Gender							
Male	171	71.9	56.2	27.5	40	33.93–46.07	0.420
Female	23	65.2	56.5	46.3	60	10.97–109.0	
Age (years)							
≤40	20	74.1	52.9	21.2	37	16.00–58.00	0.652
40–60	118	70.1	58.4	28.1	44	36.95–51.05	
>60	56	72.5	52.6	36.7	42	29.03–54.97	
Child-Pugh classification							
A	123	80.2	65.6	36.2	55	46.00–63.99	0.000
B	68	55.9	40.6	18.4	44	33.88–54.12	
C	3	51.9	38.9	0	14	6.14–21.86	
HBsAg/HCV							
(+)	173	73.6	57.0	29.3	42	35.21–48.79	0.535
(−)	21	51.0	51.0	34.0	44	0.00–94.96	
Liver cirrhosis							
Present	169	71.6	57.0	29.3	44	36.26–51.74	0.870
Absent	25	68.0	51.2	35.8	37	10.96–63.04	
Tumor differentiation							
Well	101	91.8	85.8	57.8	66	61.31–70.69	0.000
Moderate	51	69.8	42.5	6.6	32	21.89–42.11	
Poor	42	36.0	18.1	0	10	8.9–11.1	
Tumor size (cm)							
≤3	137	76.6	61.1	33.2	40	30.55–49.24	0.617
>3	57	64.1	52.1	27.5	60	35.11–59.26	
Pretreatment serum AFP (ng/ml)							
≤20	102	73.9	52.8	31.1	38	28.63–47.37	0.900
>20	92	68.1	60.0	28.5	44	37.57–50.43	
VEGF							
(++)	58	56.9	32.8	17.2	31	22.36–40.93	0.000
(+)	60	70.0	55.0	30.0	36	24.69–45.86	
(−)	76	82.7	77.2	46.2	59	49.78–68.22	
bFGF							
(++)	62	74.2	54.8	32.3	38	31.09–48.12	0.978
(+)	66	71.2	57.8	36.4	41	32.66–48.98	
(−)	66	67.5	59.2	29.2	44	34.04–53.96	
c-Met							
(++)	63	57.1	36.5	12.7	29	23.24–34.46	0.000
(+)	66	74.2	57.8	22.7	35	27.75–45.25	
(−)	65	82.0	77.4	61.6	67	59.73–74.27	
Total bilirubin (μmol/l)							
≥21.0	89	73.5	54.2	31.0	42	30.81–53.19	0.621
<21.0	105	69.2	58.0	28.9	44	36.79–51.21	
Albumin (g/l)							
≥50	66	72.1	51.1	32.1	37	28.64–45.36	0.810
<50	128	70.6	58.9	28.8	44	36.84–51.16	
Therapy method							
HR	80	68.5	60.0	25.6	48	37.57–58.43	0.488
MA	114	72.8	54.0	33.0	46	37.31–54.69	

$P<0.05$ implied statistical significance

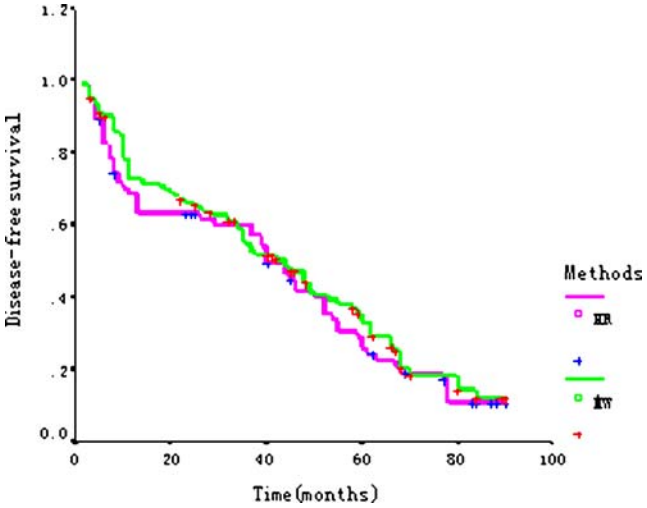

Figure 9 Disease-free survival between patients after HR and those after MA. The difference in survival rates between patients after HR and patients after MA has no statistical significance. (P=0.488).

In MA group, 30 patients died of HCC and its complications, 5 patients died of non-hepatic diseases. Causes of deaths were as follows: variceal bleeding or liver failure in 20 cases, progression of HCC in 10 cases, cardiopulmonary distress in 1 patient, renal failure in 1 patient, lung infection in 2 patients, and cerebral hemorrhage in 1 patient. In HR group, 24 patients died of HCC and its complications, 4 patients died of non-hepatic diseases. Causes of deaths were as follows: variceal bleeding or liver failure in 18 cases, progression of HCC in 6 cases, cardiopulmonary distress in 2 cases, heart attack in 1 patient, renal failure in 1 patient.

Complications of Microwave Ablation and Hepatic Resection

In MA group, most patients experienced mild to severe pain at the insertion site, or diaphragm irritation with right shoulder tip pain during the procedure. The pain lasted 1–7 days after microwave ablation and relieved in 70 patients. Only 15 patients (13.2%) required the administration of Somedon (Yongkang Pharmaceuticals, Beijing, China) twice a day 1–3 days after microwave ablation. Fever of 37.2–39.7°C began on the day of microwave ablation and persisted for 3~5 days in 78 patients (68.4%). In 6 of 12 patients in whom lesions were located in the dome of the liver, pleural effusion was observed on sonography after 1~2 days. All cleared up after 1~8 weeks. In the majority of patients, transaminase levels increased two to eight times over baseline during the first 3 days after microwave therapy. Moreover, a slight increase in total bilirubin and unconjugated bilirubin were observed in 68 patients. All of these tests decreased to preoperative levels by 7 to 10 days. No significant changes on other test results were observed. No severe complication was observed.

In HR group, 58 patients (72.5%) experienced mild pain at the cutting edge. Fever of 37.4–39.6°C began on the day of hepatic resection and persisted for 3~5 days in 16 patients (20.0%). In the majority of patients, transaminase levels increased two to eight times over baseline during the first 3 days after hepatic resection. Moreover, a significant increase in total bilirubin and unconjugated bilirubin were observed in 72 patients. All of these tests decreased to preoperative levels by 7 to 10 days. No severe complication was observed.

Prognostic Factors for Small HCC Less Than 5 cm in Diameter

Univariate Analysis

The results of univariate analysis revealed that the prognosis of HCC less than 5 cm in diameter was significantly correlated with Child-Pugh classification, tumor differentiation, expressions of VEGF, and c-Met (Figs. 5, 6, 7, 8; Table 4); whereas, there was no significant relationship between prognosis and methods of therapy (Fig. 9), gender, age, HBsAg/HCV, liver cirrhosis, serum AFP level, expressions of bFGF in tumor, total bilirubin, and albumin level.

Multivariate Analysis

The results of multivariate analysis revealed that the prognosis of HCC less than 5 cm in diameter was significantly correlated with tumor differentiation, expressions of VEGF and c-Met (see Table 5), whereas Child-Pugh classification had no significant impact on prognosis in multivariate analysis.

Table 5 Cox's Proportional Hazards Model

Variable	SE	t value	95% confidence interval	P value
VEGF	0.186	14.974	0.337–0.700	0.000
c-Met	0.214	10.890	0.324–0.750	0.002
Child –Pugh classification	0.186	0.593	0.801–1.663	0.356
Tumor differentiation	0.130	73.883	2.374–3.957	0.000

P<0.05 implied statistical significance

Discussion

HCC is one of the most common malignancies worldwide. But prognosis of HCC remains unsatisfactory because of a high incidence of recurrence.[16] In Nobuhiko's study,[17] the 3- and 5-year disease-free survival percentages of small HCC (diameter < 3 cm) after hepatic resection were 49 and 30%, respectively. In our study, 1-, 3-, and 5-year disease-free survival rates of small HCC are 71.3, 57.0, and 32.5%, respectively. Therefore, elucidation of the prognostic factors of recurrence and of the prevention and treatment strategies for small HCCs may be the most important for achieving better prognosis after treatment.

Venous invasion was found to be the most consistently reported risk factor of recurrence after resection of HCC, indicating that extrahepatic or intrahepatic metastasis is an important mechanism of postoperative recurrence.[18] Angiogenesis promotes cancer metastasis, and hence up-regulates expression of angiogenic factors may play a major role in the metastatic potential of HCC.

Recent data have implicated the involvement of VEGF, bFGF, and c-Met in the progression of HCC.[19,20] Therefore, it is of considerable interest to elucidate the role of these three factors as biological markers of tumor invasiveness in HCC patients. In our study, immunohistochemistry showed that similar to the other studies,[21–23] VEGF, bFGF, and c-Met expressed more commonly in cancerous tissues than in pericancerous tissues. This implied that they might participate in the metastasis and recurrence of small HCC. Then we enrolled them into the prognostic factors in our study.

Microwave ablation, which is developed as a minimally invasive thermal therapy for HCC, has been performed as a reliable alternative to hepatic resection in patients with small HCC.[24] Hepatic resection and liver transplantation are effective ways for treatment of small HCC, but they are much more invasive and costly.[25] In recent years, more and more patients preferred microwave ablation to hepatic section, and good curative effect has been acquired in our institution.[26] Promising results of microwave ablation for HCC have been demonstrated in several other studies.[27–30] However, there are few papers concerning the effect of microwave ablation on the recurrence and metastasis of HCCs on long-term survival, especially for small HCCs of diameter <5 cm. In this study, we compared the recurrence and metastasis of small HCCs of diameter <5 cm between microwave ablation and hepatic resection group. Our results demonstrated that compared to hepatic resection, microwave ablation could achieve nearly the same long-term disease-free survival rate. Microwave ablation was a local ablation method, and we could see local regrowth in 15 patients. But with the development of monitoring methods, such as contrast enhanced ultrasonography, the number of local residual tumor might become much less.[31]

In present study, we enrolled tumor-related factors, patient-related factors and therapeutic methods (MA or HR) as prognostic factors. Four variables (Child-Pugh classification, degree of tumor differentiation, expression of VEGF and c-Met) were found to be important risk factors impacting disease-free survival rate in univariate analysis. However, univariate analysis does not always reflect the actual significance of a factor, multivariate analysis that considers multiple variables simultaneously was further applied. Only three variables (degree of tumor differentiation, expression of VEGF and c-Met) were shown to have independent prognostic value by multivariable analysis. Child-Pugh classification lost its significance because of the overpowering influence of the other three factors. Then we can see that angiogenesis plays an important role in the metastasis and recurrence of HCC.

Statistical results showed that disease-free survival rates were not significantly influenced by age, gender, HBsAg/HCV, accompany liver cirrhosis, serum AFP level, expression of bFGF in cancer tissues, and serum level of total bilirubin and albumin. The study of Nobuhiko[17] revealed that age more than 60 years was the independent unfavorable prognostic factor affecting disease-free survival, which was not coincident with ours. Maybe this was caused by the facts that the definitions of small HCCs and the predictors chosen in these two studies were not the same.

In our study, patients in MA group have no significant difference with patients in HR group in age, gender, HBsAg/HCV, accompany liver cirrhosis, serum AFP level, the expression of bFGF in cancer tissues, serum level of total bilirubin and albumin. The 1-, 3-, and 5-year disease-free survival rates in MA group were similar to those of HR group. The therapeutic method could not be one of the prognostic factors of small HCC. This also demonstrated that microwave ablation, although as a minimally method, can acquire a good clinical effect.

Angiogenesis, or the development of a vascularized stroma, is essential for tumors to grow beyond a minimal size and metastasis. Even small HCC can be discovered to have micrometastases.[32] Yoshiji et al.[33] used an elaborated experimental setting to prove the effect of VEGF on HCC growth. They found overexpression of VEGF in vivo resulted in increased neovascularization and tumor size. Ueki et al.[34] examined HGF concentration and expression of the c-Met in 62 patients with HCC to determine the relationship between the level of expression and clinicopathological features, and patient outcome after hepatectomy. The results were that there was no correlation between HGF concentration in the tumor tissue and clinicopathological factors and patient survival, while patients with high c-met HCC had a significantly shorter 5-year survival than patients with low c-met HCC. These results indicated that expression of c-met played an important role in tumor growth and

metastases in patients who underwent hepatectomy for HCC. Our results further demonstrated that VEGF and c-Met played an important role in the metastasis and recurrence of HCC, even in small HCC. The expression of VEGF and c-Met may facilitate the micrometastasis of tumor cells, that is to say that tumor cells might have broken through the capsule of HCC before treatment. This leads to a 'completed resection or ablation' of a tumor in imaging, but the micrometastasis can develop to a new tumor (recurrence) in a certain time.

Although bFGF was demonstrated to have close relation with post operative recurrence HCC,[35] it did not have correlation with recurrence and metastasis in small HCC in our study. This might be because the indices used in these two studies were not same. Our attention was on the expression of bFGF in cancerous tissues, while their attention was on the level of serum bFGF. In addition, these two studies had different enrollment criteria (small HCC in our study). But all these need more studies to be demonstrated.

Our study was a retrospective study. It could not avoid some biases. And because most of the specimens acquired from biopsy had no pericancerous tissues, we could only make use of the specimens acquired from hepatic resection to analyze the differentiation of the expressions of VEGF, bFGF, and c-Met between cancerous tissues and pericancerous tissues.

In conclusion, in patients with small HCC, less than 5 cm in diameter, tumor differentiation, and expressions of VEGF and c-Met can be as the prognostic factors of metastasis and recurrence. HCCs of low differentiation, and expression of VEGF or c-Met often have more chances of recurrence. Microwave ablation, as a minimally invasive treatment, may achieve similar clinical effect compared to hepatic resection while not increase the metastasis and recurrence rate. But because our study is not a randomized study, further prospective study with continuous patients in both MA group and HR group is needed to demonstrate our conclusion.

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Right Hepatic Lobectomy Using the Staple Technique in 101 Patients

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Abstract

Background Application of linear stapling devices for extrahepatic vascular control in liver surgery has been well-established. However, the technique for use of stapling devices in hepatic parenchymal transection is not well defined.

Purpose To describe the safety and efficacy of our technique for use of vascular stapling devices in hepatic parenchymal transection during open right hepatic lobectomy is the purpose of this study.

Methodology We reviewed our experience with 101 consecutive open right hepatic lobectomies performed by a single surgeon between January 2003 and July 2006, in which vascular staplers were utilized for the parenchymal transection phase.

Results Of the 101 patients who underwent resection, 53 (52%) were female. The mean age was 58 years. Malignant disease was the indication for resection in the majority of patients (88%). Of those with cancer, 78% (69 of 89) had metastatic colorectal cancer, 6% (5 of 89) had metastatic neuroendocrine tumor, 4% (4 of 89) had hepatocellular carcinoma, 4% (4 of 89) had cholangiocarcinoma, and the remaining 8% were other metastatic cancers. Twelve patients (12%) underwent resection for hepatic adenoma or symptomatic benign disease (FNH or hemangioma). Forty-eight patients (48%) underwent a major ancillary procedure at the time of hepatic resection. Thirty-nine patients (39%) had a nonanatomic wedge resection of a left lobe lesion, 27 patients (27%) had one or more lesions treated with radiofrequency ablation (RFA), and 6 patients (6%) were treated with a synchronous bowel resection. The median total operative time was 336 min (range 155–620 min). A Pringle maneuver for temporary vascular inflow occlusion was utilized in all cases, with a median time of 9 min (range 4–17 min). Ten patients (10%) required blood transfusion during surgery or in the postoperative period. The maximum transfusion was 2 U of packed red blood cells (PRBC) in seven patients and 1 U of PRBC in three patients. The mean nadir postoperative hematocrit was 28.2. All patients with malignant disease had tumor-free margins at the completion of the procedure. The average hospital length of stay was 6.0 days. One patient (1%) developed a clinically significant bile leak requiring a postoperative endoscopic retrograde cholangiography (ERCP). No patient required reoperation. The 30 and 60-day postoperative survival was 100%.

Conclusion These findings indicate that application of vascular stapling devices for parenchymal transection in major hepatic resection is a safe technique, with low transfusion requirements and minimal postoperative bile leak. The technique allows for rapid transection of the entire right hepatic lobe in under 10 min. Short video clips of the technique will be demonstrated.

Keywords Hepatectomy · Surgical staplers · Liver cancer

Introduction

Historically major hepatic resections (hemihepatectomies) were associated with significant morbidity and mortality, most notably related to intraoperative blood loss.[1] Over the

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course of the past few decades, improvement in surgical techniques and technology both have contributed to reducing the risk of significant bleeding. These improvements have translated into mortality rates of under 5% in specialized centers, even for the most extensive resections.[1] Improved surgical techniques stem from enhanced understanding of hepatic anatomy and improved preoperative imaging. At the same time, technological advances have provided liver surgeons with an armamentarium of hemostatic devices that can be utilized during liver resections.[2]

Use of vascular staplers for safely securing and dividing inflow and outflow vessels in major liver resections is well described in the literature.[3–12] This vessel stapling technique is quick and can decrease the risk of hemorrhage that can be associated with dividing a major hepatic or portal vein branch. Application of surgical stapling devices for parenchymal transection in hepatic surgery is not well described in the literature. Originally, reports only described a stapling technique for minor hepatectomies.[13,14] More recently, there has been reports of transparenchymal application of vascular linear cutting staplers to divide the inflow pedicle and transect the parenchyma in major hepatectomies.[15,16] We sought to review our experience with 101 major hepatectomies (right hemihepatectomy) in which the stapling technique was utilized for the entire parenchymal transection phase.

Methods

After obtaining approval from The University of Pittsburgh Institutional Review Board, we analyzed our prospectively established liver cancer data base. One hundred and one elective right hemihepatectomies performed by a single surgeon between January 2003 and July 2006 were selected. A stapling technique was utilized for the entire hepatic transection phase in all cases. Data extracted included demographics, diagnosis, ancillary procedure, laboratory values, blood transfusions, procedure time, Pringle time, length of stay, and major complications.

Surgical Technique Hepatic resection is performed through a right subcostal incision with midline extension. The liver is mobilized by division of the falciform and right triangular ligaments. Intraoperative ultrasonography is utilized to identify lesions, delineate the vascular anatomy, and mark the transection plane through Cantlie's line. If the gallbladder is present, a cholecystectomy is performed and the parenchymal transection is followed by a completion cholangiogram through the cystic duct stump. The liver is elevated from the inferior vena cava, and all short hepatic veins are secured with silk tie ligation or hemoclips. The right hepatic vein is divided with a US Surgical Endo GIA™ vascular stapler under direct visualization. We preferentially use the white, roticulating 45 mm vascular load for this step (video 1). Next, the right hepatic artery is ligated and divided outside the liver in the hepatic hilum. The extra-hepatic right portal vein is then divided in the hepatic hilum with the same vascular stapler. Before dividing the right hepatic duct and hilar plate, the caudate isthmus is notched to facilitate passing a blunt Kelly clamp from the right side of the base of the gallbladder fossa behind the hilar plate to emerge anterior to the IVC. The flat end of the US Surgical Endo GIA™ stapler is then passed through this tunnel to divide the hilar plate and right hepatic duct (video 2). With this maneuver, the right anterior and posterior hepatic ducts are usually divided separately about 1 cm to the right of the right/left bifurcation. Using Bovie electrocautery the liver capsule is scored along a previously marked transection plane. The dissection is then extended to a depth of 1–2 cm into the hepatic parenchyma using the Bovie cautery and TissueLink™ (cone head). Next, a Pringle maneuver is applied with a vessel loop around the hepatoduodenal ligament and secured with a right angle clamp. A long Kelly clamp is then used to create sequential tunnels in the hepatic parenchyma. Tissue resistance during the tunneling maneuver provides critical feedback for safe placement of the stapler to avoid tearing crossing middle hepatic vein branches. After each pass of the Kelly clamp, an Ethicon EZ45™ linear stapler is then deployed to sequentially divide the liver parenchyma (video 3). Typically, eight to ten cartridges are required to completely transect a thick right hepatic lobe. This stapler is utilized for the parenchymal transection phase because it is a one-handed crushing stapler that allows the surgeon to use his/her other hand to protect the inferior vena cava as the stapler is applied. The Pringle clamp is then released, and complete hemostasis on the cut parenchyma is achieved with TissueLink™ (conehead) and occasional figure-of-eight suture. Any obvious bile leak seen on the cut surface during completion retrograde saline cholangiogram is closed with suture. Intraoperative gross negative margins are verified in all cases by pathology. A closed-suction bulb drain is placed in all cases next to the cut edge of the liver, and the left lobe is tacked back up to the anterior abdominal wall at the falciform ligament. Completion ultrasonography is performed to confirm vascular inflow and outflow of the remaining left lobe.

Results

Indications and Ancillary Procedures

Between January 2003 and July 2006, 101 elective right hemihepatectomies were performed at the Liver Cancer

Table 1 Indications for Right Hemihepatectomy in 101 Patients

Liver lesion	Number of patients
Benign	12
Hemangioma	7
Focal nodular hyperplasia	2
Hepatic adenoma	1
Liver abscess	2
Malignant	89
Colon/rectal cancer metastasis	69
Neuroendocrine tumor	5
Hepatocellular carcinoma	4
Cholangiocarcinoma	4
Breast cancer metastasis	3
Sarcoma	1
Thyroid cancer metastasis	1
Anal cancer metastasis	1
Lung cancer metastasis	1
Total	101

Center-University of Pittsburgh Medical Center, by a single surgeon. There were 53% female, and the mean age was 58 years. Malignant disease was the indication for resection in the majority of patients (88%—89 of 101) (Table 1). Of those resected for malignant disease the majority had metastatic colon/rectal cancer (78%—69 of 89).

The most common indication for benign resection was symptomatic hemangioma (58%—7 of 12) (Table 1). All 101 patients underwent a formal right hepatic lobectomy, and 48% (48 of 101) underwent one or more major ancillary procedures at the time of hepatic resection (Table 2). The most common ancillary procedure performed was a nonanatomic wedge resection of a left hepatic lobe lesion (39%—39 of 101).

Inflow Occlusion and Total Operative Times

Routinely, the right hepatic vein and right portal vein were divided outside the liver. Immediately before starting the stapled parenchymal transection, Pringle maneuver was applied as described above. As such, in this series, the Pringle time closely approximates the time for parenchymal transection. The median Pringle time was 9 min (range 4–17 min), and the median total operative time was 336 min (range 155–620 min). Table 3

Table 2 Ancillary Procedures Performed at the Time of Hepatic Resection

Ancillary procedure	Number of patients
Nonanatomic wedge resection of a left hepatic lobe lesion	39
One or more hepatic lesions treated with radiofrequency ablation (RFA)	27
Synchronous bowel resection	6

Table 3 OR Times Median Minutes

Parameters	Values
Procedure time-median minutes(range)	336 (155–620)
Right hepatic lobectomy only procedure time-median minutes (range)	308 (171–620)
Pringle time-median minutes (range)	9 (4–17)

Blood Loss and Blood Transfusions

Ten patients required blood transfusion during surgery or in the immediate postoperative period (Table 4). The maximum transfusion volume was 2 U of packed red blood cells (PRBC) in seven patients, and 1 u of PRBC in three patients. Typical estimated blood loss (EBL) was 150 ml; however, we recognize that estimating blood loss in a major abdominal procedure tends to be an inexact measurement. Therefore, to obtain a more accurate measurement of intraoperative blood loss, we extracted preoperative, and nadir postoperative hematocrit values. The mean preoperative hematocrit (Hct) was 39.7, the mean nadir postoperative Hct was 28.2. In the subgroup that did not receive any blood products (90%—91/101) the mean preoperative Hct was 40.4, the mean nadir postoperative Hct was 28.6. In the subgroup of patients that did require blood transfusions ($n=10$) the mean preoperative Hct was markedly lower at 34.0. These patients were typically anemic due to prior systemic chemotherapy. To maintain low central venous pressure (CVP), patients routinely received minimal fluids during the procedure until the right lobe specimen was removed. Some of the change in Hct reflects hemodilution due to intraoperative and postoperative resuscitation with intravenous fluids.

Length of Stay, Complications, and Margins

The mean length of stay was 6 days (range 2 days–19 days) (Table 5). Bile leak was reported if there was evidence of any bile tinge in the JP drain after the first postoperative

Table 4 Blood Loss and Transfusion

Parameters	Values
Transfusion rate	10%
Maximum transfusion volume	2 uPRBC
Transfusion volume distribution	
1 uPRBC	3 patients
2 uPRBC	7 patients
Preoperative Hct nontransfused subgroup (mean)	40.4
Preoperative Hct transfused group (mean)	34.0

Table 5 Outcomes

Parameters	Values
Length of stay–median days (range)	6 (2–19)
Clinically significant bile Leak	1%
Gross negative margins	100%
Postoperative hemorrhage requiring reoperation	0%
30-day mortality	0%
60-day mortality	0%

day. One patient (1%—1/101) developed a clinically significant postoperative bile leak requiring endoscopic retrograde cholangiography (ERCP), which was successful in sealing the leak. There were no episodes of postoperative hemorrhage or reoperation. There were no episodes of postoperative liver failure. The 30- and 60-day postoperative survival was 100%. All patients with malignant disease had grossly negative margins by intraoperative pathology assessment (see Fig. 1).

Discussion

Specialized high volume centers of excellence have made remarkable progress in major liver resections over the past few decades. This progress stems from multiple improvements in preoperative assessment, intraoperative technique, and postoperative care.[17] Improved preoperative assessment is based on overall understanding of patients' ability to tolerate major abdominal surgery, improved evaluation of liver function and hepatic reserve, and enhanced preoperative imaging. These factors all equate to ideal patient selection. Improved postoperative care is founded on advances in monitoring, and image guided minimally invasive therapeutics that avoid reoperative surgery. Nonetheless, just as it was described in the first reports of liver resections, concerns regarding major intraoperative hemorrhage and the complications thereof still pose an issue today.

The application of vascular stapling devices has previously been shown to be a safe method for controlling the hepatic and portal veins.[3–12] Hemorrhage during hepatic parenchymal transection can result in steady and not insignificant bleeding. The traditional technique of clamp crushing and tie ligation can be associated with constant oozing. Even though a wide array of electrosurgical and hemostatic instruments for hepatic transection have provided tools of minimizing blood loss in liver surgery, the potential blood loss during parenchymal division can still be significant, particularly due to ongoing back bleeding from the middle hepatic vein branches. Based on the reports of successful stapling of extrahepatic vessels, we have applied stapling devices to parenchymal transection. One of the advantages of the stapling technique is the speed in which the transection can be performed thus minimizing the surface bleeding and the warm ischemia (Pringle time) for the remnant liver.

In both open and laparoscopic procedures, surgeons have been extending the application of stapling technology to an increasing number of procedures.[18–29] Surgical staplers have become a vital tool in most hollow organ abdominal surgery; however, application in solid organ surgery is not widely described. Pancreatic surgeons have extended the routine use of stapling devices in solid organ surgery in laparoscopic distal pancreatectomies.[30] Based on our series, we propose that stapling technology is ideally suited for parenchymal transection in major hepatectomies. With the technique described above, Pringle time approximates parenchymal transection time. In 101 right hepatic lobectomies, a very short median Pringle time of 9 min minimized the time of surface bleeding, and warm ischemia time to the remnant liver. The technique of a stapled hepatectomy is a dynamic process of rapid sequential tunneling and stapler applications. Once the specimen is removed, the remnant liver cut edge can be rapidly

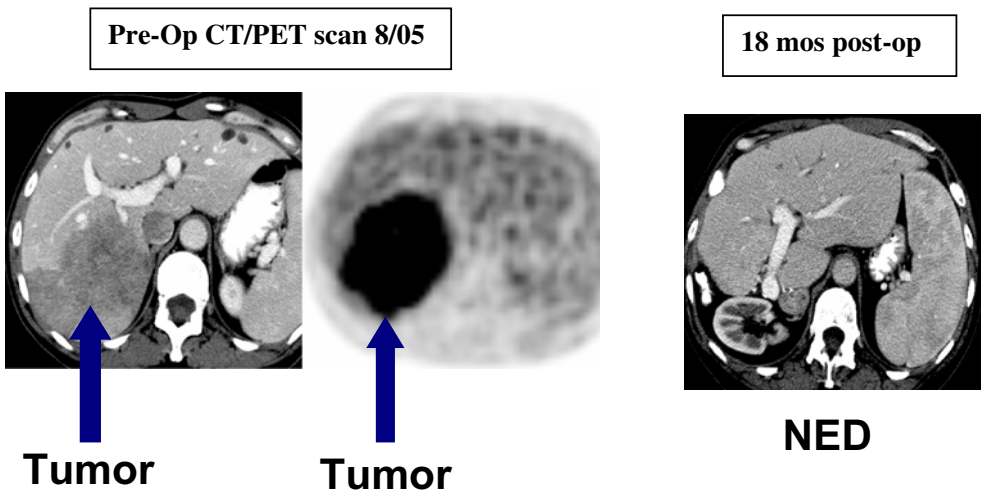

Figure 1 Right hepatic lobectomy using staple technique.

inspected, and any necessary hemostatis achieved with an electrosurgical device or occasional suture ligation. In our series, only ten patients required transfusion, and the maximum transfused volume never exceeded 2 U PRBC.

The other significant cause for morbidity in liver resection relates to postoperative bile leak. As a closed-suction bulb drain was placed in all patients in this series, we had an opportunity for early detection of biliary leak. We defined a clinically significant bile leak as any bile tinge in the JP drain after the first postoperative day. Only one patient (1%—1/101) developed a clinically significant bile leak that required ERCP and stent placement for resolution. This low bile leak rate may be attributed to multiple factors, including, (1)sealing of any potential secondary biliary readicals with the staple cartridges, (2) TissueLink™ application to the entire cut liver edge, and (3) intraoperative saline completion cholangiogram with oversewing of any detected bile staining on the cut edge.

Adherence to oncologic principles is the key to minimizing local recurrence and improving survival in liver resections for malignant disease. Concerns might be raised regarding precision of the stapled hepatectomy technique, as it relates to the ability to rapidly divide the liver with tumor-free margins. By scoring the liver capsule and confirming an oncologically appropriate transection plane with intraoperative ultrasonography, we were able to achieve tumor free margins in all 89 patients with malignant disease.

Perhaps the one major disadvantage of the stapled hepatectomy technique is the cost of multiple stapler cartridges. However, issues of cost related to this technique should be weighed against the expenses associated with ICU admission, blood transfusion, and OR time, which if minimized, potentially offsets the cost of the staple cartridges.

Conclusion

In summary, we report a large series of a stapled hepatectomy technique, and demonstrate it to be a safe, rapid, and hemostatic method of dividing the entire liver parenchyma without an increased risk of postoperative bile like or compromised oncologic margins.

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ORIGINAL ARTICLE

The Glucagon Provocative Test for the Diagnosis and Treatment of Zollinger–Ellison Syndrome

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Abstract
Objective Our aim was to determine whether the glucagon provocative test could be used in place of secretin test in patients with gastrinoma.
Methods Three patients with gastrinoma underwent the following examinations: (1) preoperative intravenous glucagon test to enable a definitive diagnosis, (2) intra-arterial glucagon injection test to localize the tumor, and (3) intraoperative and postoperative intravenous glucagon test to confirm the completeness of the resection.
Results Serum gastrin levels increased in response to intravenous glucagon in all three patients preoperatively. Computed tomography scans revealed a tumor in the lesser omentum, pancreatic head, and the pancreatic uncinate in cases 1, 2, and 3, respectively. Intra-arterial glucagon test revealed that the feeding artery for the tumor was the left gastric artery in case 1 and the superior mesenteric artery in case 3. Resection of the remnant stomach with tumor, pancreaticoduodenectomy with portal vein resection, and enucleation of the tumor were performed in cases 1, 2, and 3, respectively. Serum gastrin levels did not increase in response to intravenous glucagon intraoperatively and postoperatively in cases 1 and 3. Although intravenous glucagon caused a slight increase in serum gastrin in case 2, no recurrent tumors were evident.
Conclusion These results indicate that the glucagon provocative test is a suitable alternative to testing with secretin, which is not commercially available in Japan.

Keywords Gastrinoma · Glucagon · Secretin

Case 1 in this study was published as a case report in Japanese in Jpn J Gastroenterol Surg 2007; 40:1582-1586.

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Introduction

The role of the secretin provocative test is well established in the diagnosis of gastrinoma (Zollinger–Ellison syndrome, ZES), i.e., a paradoxical increase in plasma gastrin levels after intravenous (i.v.) injection of secretin is useful in definitively diagnosing gastrinoma.[1] Localizing tumors is often difficult in ZES because of their small size, although the diagnosis of gastrinoma is made based on the i.v. secretin test. Somatostatin receptor scintigraphy (SRS) is believed to be the best imaging modality for localizing gastrinomas.[2] The SRS examination, however, is unfortunately not available in Japan. The selective arterial secretin injection (SASI) test proposed by Imamura et al.[3] is reported to have high specificity in localizing gastrinomas. One disadvantage of the SASI test is that it is invasive and necessitates the use of celiac angiography. However, an advantage of the SASI test is that it is able to localize gastrinomas at the level of the feeding artery and is,

therefore, useful for determining the optimal operative procedure.[4] Secretin is difficult to obtain in Japan and other countries.[5] Therefore, an alternative agent that can be used in place of secretin is needed. Intra-arterial (i.a.) as well as i.v. calcium injection test is also useful for diagnosing gastrinomas,[6] although calcium test is not specific for the diagnosis of gastrinoma. Our group and other investigators have reported that i.v. injection of glucagon evokes an increase in plasma gastrin in patients with ZES.[7,8]The aim of this report was to study the usefulness of i.v. and i.a. glucagon provocative tests for diagnosis, tumor localization, and treatment in patients with ZES.

Patients and Methods

Three patients suspected to have ZES because of duodenal ulcer, high serum gastrin, and intraabdominal tumor underwent the glucagon (Glucagon-G Novo, Eisai Pharmacy, Tokyo, Japan) provocative test. For the preoperative glucagon test, glucagon was administered i.v. at a dose of 20 μg/kg plus 20 μg kg^{-1} h^{-1} for 1 h in three patients to diagnose ZES. Serum gastrin was measured 1 and 3 min before and 3, 5, 10, 20, 30, 40, 50, and 60 min after administration in case 1. In cases 2 and 3, serum gastrin was measured 1 and 3 min before and 3, 5, 7, 10, 15, 20, 30, 40, 50, and 60 min after administration.

In cases 1 and 3, i.a. glucagon test was used to localize tumors and was performed using the same method as for the SASI test;[3] under angiographic technique, blood samples were withdrawn from the hepatic vein 60 s before and 20, 40, 60, 120, and 180 s after i.a. glucagon injection. If serum gastrin increased by more than 80 pg/ml within 40 s to at least 20%, that artery was considered the feeder.[9] Intraoperative i.v. glucagon testing to assure the completeness of the resection was performed in cases 1 and 3; blood samples were withdrawn immediately after the resection and three times every 10 min. Glucagon (20 μg/kg) was then injected as a bolus about 30 min after the extirpation of the tumor, and blood samples were taken 3, 5, 10, 15, and 20 min after glucagon administration. Postoperative i.v. glucagon test was performed in three patients 3 to 4 weeks after the operation using the same method as was used for the preoperative i.v. glucagon test.

For the intraoperative i.v. glucagon test, serum gastrin levels were measured using a commercially available radioimmunoassay kit (Gastrin RIA Kit II, Kyowa Medex, Tokyo, Japan). For the measurement of serum gastrin levels in the intraoperative i.v. glucagon test, the incubation time was shortened from 1.5 h to 30 min so that the results could be determined as soon as possible. We measured serum gastrin levels after 1.5-h, 1-h, 30-min, and 15-min incubations beforehand and ascertained that serum gastrin levels measured after a 30-min incubation did not differ from the levels measured after a 1.5-h incubation.[10] The abdominal wall was closed after the results of the intraoperative i.v. glucagon test were obtained. The results of histologic examinations confirmed that all three patients had gastrinoma.

Results

Case 1 A 74-year-old woman underwent simple closure of a perforated duodenal ulcer as an emergency operation 15 months before referral to us. Although she was taking a histamine-2-receptor blocker thereafter, the duodenal ulcer recurred 1 year later and caused duodenal bleeding. In the second emergency operation, distal gastrectomy with Billroth-II reconstruction was performed after ligating the gastroduodenal artery for hemostasis. She was referred to our hospital for examination because of high (1,850 pg/ml) serum gastrin levels (Table 1). Serum gastrin levels increased to 2,270 pg/ml from 1,700 pg/ml 10 min after injection (a 34% increase) in the preoperative i.v. glucagon

Table 1 Clinical Features of Three Patients

	Age, Sex	Past Surgery for Duodenal Ulcer	Site of Duodenal Ulcer	Fasting Serum Gastrin (pg/ml)	Preoperative i.v. Glucagon Test	Site of Tumor	Feeding Artery[a]	Performed Procedure	Postoperative i.v. Glucagon Test
1	74, F	1. Simple closure 2. Distal gastrectomy	Bulb	1,850	Positive	Lesser omentum	Lt. gastric artery	RRST[b]	Negative
2	53, M	None	Bulb	8,460	Positive	Pancreatic head	Not investigated	SSPPD[c]	Not determinable
3	56, F	None	Descending portion	709	Positive	Pancreatic uncinate	SMA	Tumor enucleation	Negative

[a] Judged from i.a. glucagon test
[b] Resection of the remnant stomach with tumor
[c] Subtotal stomach-preserving pancreaticoduodenectomy

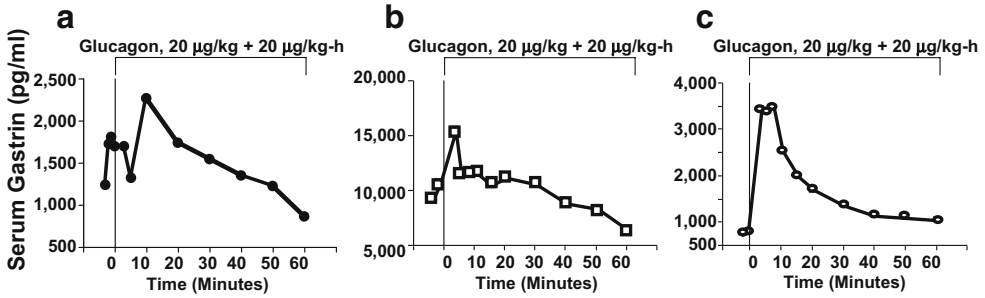

Figure 1 Results of preoperative i.v. glucagon test in cases 1 (**a**), 2 (**b**), and 3 (**c**). Serum gastrin levels increased in all three patients in response to glucagon 3 to 10 min after administration. The percentage increase compared to baseline values was the highest in case 3 (329%), whereas the increase in cases 1 and 2 were around 30 to 70%.

test (Fig. 1a). A computed tomography (CT) scan revealed a tumor (4×4 cm) in the lesser omentum. No other tumor was found in the region of the so-called gastrinoma triangle. The tumor was stained on left gastric arteriography. Glucagon (30 μg) was injected as a bolus via a catheter introduced into either the superior mesenteric artery (SMA), splenic artery, common hepatic artery, or left gastric artery in this order. When glucagon was injected into the left gastric artery, the serum gastrin level in the hepatic vein increased to 1,410 from 1,020 pg/ml as the basal value, therefore, the left gastric artery fulfilled the criteria as the feeder (Fig. 2a). No significant increase in the serum gastrin level in the hepatic vein was observed when glucagon was injected into the SMA, splenic artery, and common hepatic artery (Fig. 2a). Glucagon could not be injected into the gastroduodenal artery, as it was ligated at the second emergency operation. On laparotomy, no other tumors were identified despite careful intraoperative examinations, which included ultrasonography and palpation. The remnant stomach, as well as the tumor in the lesser ometum, was resected. The abdominal wall was closed after determining that the serum gastrin level did not increase in response to i.v. glucagon injected during the operation (Fig. 3a). The basal serum gastrin level was relatively elevated, but within normal range (less than 200 pg/ml), and the postoperative i.v. glucagon test revealed that glucagon administration did not increase the serum gastrin level (Fig. 4a). The patient is doing well without signs of recurrence 2 years postoperatively, and the serum gastrin level decreased to 70 to 80 pg/ml.

Case 2 A 53-year-old man had been taking a proton pump inhibitor for 7 years for the treatment of duodenal ulcer. He was referred to our hospital for examination because of a

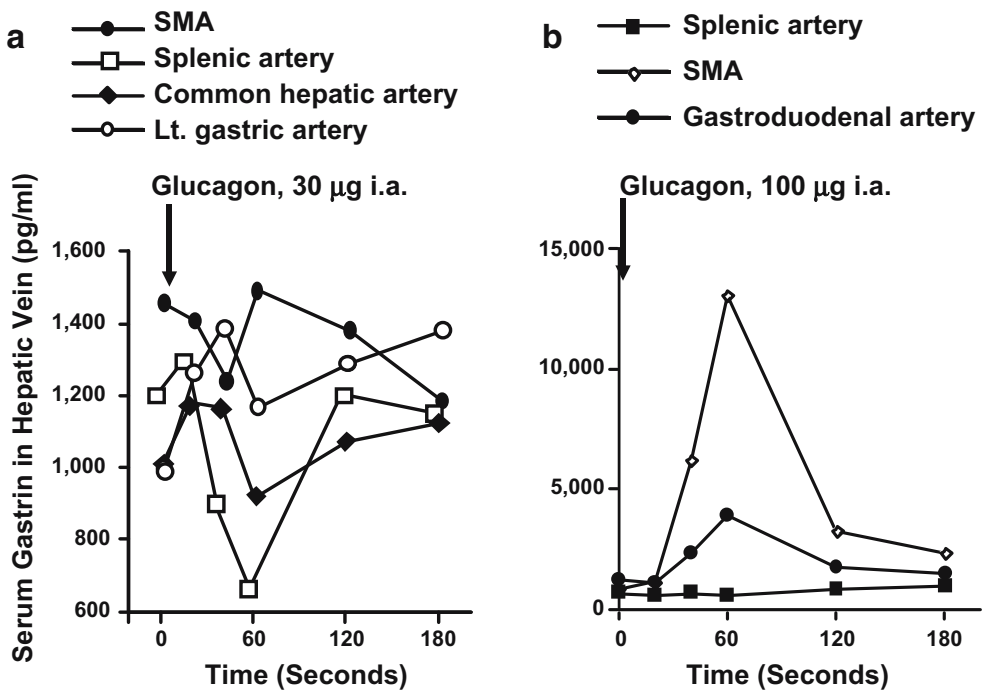

Figure 2 Results of the i.a. glucagon test in cases 1 (**a**) and 3 (**b**). **a** Serum gastrin levels increased after glucagon administration into the *left* gastric artery, but not in the other arteries. **b** Although serum gastrin levels increased after glucagon injection into the SMA and gastroduodenal artery, the SMA was considered as the main feeder for the tumor.

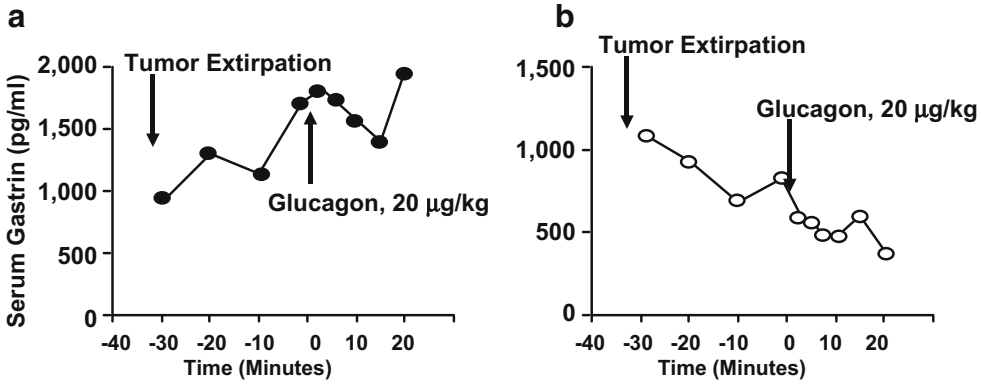

Figure 3 Results of the intraoperative i.v. glucagon test in cases 1 (**a**) and 3 (**b**). Administration of i.v. glucagon during the operations after tumor resection did not cause serum gastrin to increase in either patients.

submucosal tumor-like elevation in the duodenum identified during gastroduodenal fiberscope examination. His serum gastrin level was as high as 8,460 pg/ml at the time of referral to us (Table 1). The serum gastrin increased to 15,800 from 9,250 pg/ml 3 min after injection (a 71% increase) in the preoperative i.v. glucagon test (Fig. 1b). A CT scan revealed a tumor (3×4 cm) in the pancreatic head. Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) with resection of the portal vein was carried out. In this SSPPD, most of G cells releasing gastrin are preserved as the stomach is transected 4–5 cm proximal to the pylorus. We did not perform i.a. glucagon and intraoperative i.v. glucagon tests because it was obvious that pancreaticoduodenectomy was the only appropriate procedure in this patient. His fasting serum gastrin level decreased to around 600 to 700 pg/ml, but did not return to normal range. The serum gastrin level increased from 643 pg/ml at baseline to 833 pg/ml 3 min after injection in an i.v. glucagon test performed 6 months after the operation (a 30% increase, Fig. 4b). Increase in serum gastrin was likely due to hyposecretion of the gastric acid associated with oral intake of the proton pump inhibitor, but the possibility of recurrence could not be denied. Although his fasted serum gastrin level increased gradually, the peak value (1,072 pg/ml) did not differ from the basal value (1,050 pg/ml) in an i.v. glucagon test performed 18 months postoperatively. No recurrent tumors were detected by CT scan, magnetic resonance imaging, and positron emission tomography.

Case 3 A 56-year-old woman with duodenal ulcer in the descending portion and high serum gastrin levels was referred to our hospital (Table 1). In the preoperative i.v. glucagon test, the serum gastrin level increased from 822 pg/ml at baseline to 3,507 pg/ml (a 327% increase) 7 min after injection (Fig. 1c). A round-shaped tumor 10 mm in diameter was found in the pancreatic uncinate behind the superior mesenteric vein. Glucagon (100 μg) was injected into the splenic artery, SMA, and gastroduodenal artery in that order. Although the SMA and gastroduodenal artery fulfilled the criteria as feeders, the SMA was considered to be the main feeding artery because the extent of the increase in the serum gastrin level was much greater than for gastroduodenal artery (Fig. 2b). Intraoperative exploration including ultrasonography and careful palpation around the pancreaticoduodenal region did not reveal any tumors other the one in the pancreatic uncinate. The tumor in the pancreatic uncinate was not invasive, and enucleation of the tumor was performed. An intraoperative frozen section revealed that the tumor was an endocrine tumor and not a lymph node. The serum gastrin level decreased gradually after tumor extirpation and was not increased in response to i.v. glucagon injection during the

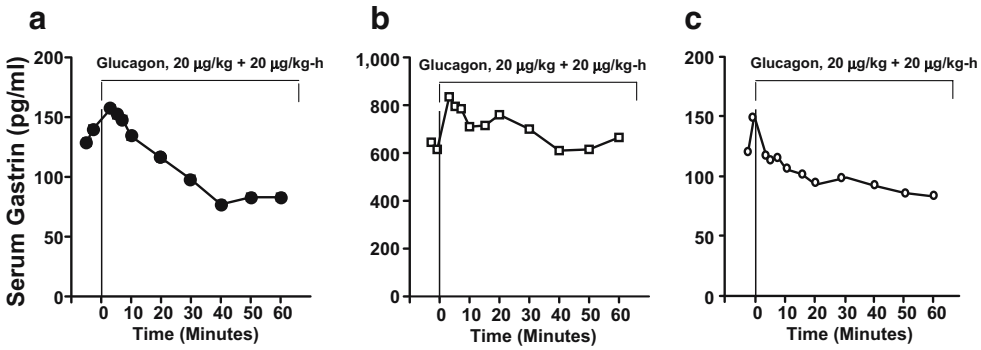

Figure 4 Results of the postoperative i.v. glucagon test in cases 1 (**a**), 2 (**b**), and 3 (**c**). Postoperative fasting serum gastrin levels decreased to within normal range and did not increase in response to i.v. glucagon in cases 1 and 3. The fasting serum gastrin level in case 2 was as high as 600 pg/ml, and i.v. glucagon increased the level to around 800 pg/ml.

operation (Fig. 3b). These results from the intraoperative glucagon test led us to the decision to close the abdominal wound after tumor enucleation only. The basal serum gastrin level was slightly increased but less than 200 pg/ml, and the postoperative i.v. glucagon test was negative (Fig. 4c). The patient has since been doing well, has shown no signs of recurrence, and the serum gastrin level has decreased to 80 pg/ml.

Discussion

In the present study, we showed the potential value of glucagon provocative test for aiding diagnosis and localization of gastrinoma. This is the first report that indicated the usefulness of i.a. glucagon test in localizing gastrinoma. Glucagon has a similar amino acid sequence to secretin and classified as belonging to the "secretin family" based on its structure. Glucagon, as well as secretin, inhibits the release of gastrin and gastric acid secretion in healthy subjects and patients with peptic ulcer disease.[11,12] Therefore, the use of the term "paradoxical increase" in the secretin provocative test can be also applied to the glucagon test. Although it is desirable to show the mechanism of glucagon to stimulate release of gastrin from gastrinoma cells, we believe that existing data already suggest the clinical usefulness of the glucagon test.

Secretin has not been available in Japan since 2004 and is difficult to obtain in other countries.[5] We considered that glucagon would be an appropriate alternative to the use of secretin because i.v. glucagon elicits a very rapid and sharp increase in serum gastrin similarly to secretin,[8] and glucagon is commercially available as an agent for inhibition of gastric motor activity during gastroduodenal fiberscopy. As another alternative to secretin, i.v. and i.a. calcium injection tests might also be useful for diagnosing and localizing gastrinoma.[5,6] A disadvantage of the i.v. calcium injection test is the delayed response of serum gastrin level as compared with glucagon and secretin; we previously reported that the increase in serum gastrin levels peaked at 3 to 4 h after calcium infusion (5 mg kg^{-1} h^{-1} for 3 h).[8] The percentage increase in serum gastrin levels was approximately 20% at 5–20 min after i.v. injection of 255 mg calcium,[6] and this increase is considerably smaller than that obtained with the secretin provocative test. The calcium injection test is non-specific with respect to the diagnosis of pancreatic endocrine tumors. We previously reported that serum gastrin levels increased after calcium injection in a patient with stomal ulcer without gastrinoma.[13] Thus, we believe that glucagon is a suitable agent for provocative test for gastrinoma.

With the glucagon provocative test, there are several issues that should be clarified: (1) the proper dose of glucagon and criteria for positive response in both the i.v. and i.a test, (2) the differential sensitivity to glucagon among patients, and (3) the use of glucagon in diabetic patients.

In the present study, glucagon was administered preoperatively using a 20 μg/kg bolus i.v. injection+20 μg kg^{-1} h^{-1} for 1-h infusion to reach a diagnosis, and this dose was determined according to previous reports.[8,13] Our results suggest that the dose of glucagon in our i.v. test is enough to induce paradoxical increase in serum gastrin level. Smaller doses than ours, however, might be enough potent to induce this response. Studying the effect of various doses of i.v. glucagon on serum gastrin level must be able to solve this issue. We used glucagon doses of 30 and 100 μg for the i.a. test in the present study. Our results in i.a. test indicate that a 100-μg dose of glucagon is appropriate, as results in case 3 were very clear. It is also controversial whether the criteria for determining the feeding artery (serum gastrin levels of >80 pg/ml and a 20% increase from baseline within 40 s after injection) in the SASI test[9] can be similarly applied to our i.a. glucagon test. Data for the i.a. glucagon test at a glucagon dose of 100 μg would be helpful for establishing the criteria for identifying.

The percentage increase in serum gastrin levels after i.v. glucagon administration varied in each patient (34, 71, and 327%) and was not related to the fasting serum gastrin level. It is obvious that case 3 was the most sensitive to glucagon in the present study. Although we have no precise explanation for the variability between patients, it is important to confirm the increase in serum gastrin levels using the i.v. glucagon test before performing the i.a. glucagon test. It could be an option to change the dose for the i.a. test depending on the percentage increase observed after i.v. injection of glucagon. The i.a. glucagon test should be avoided in patients that do not respond to i.v. glucagon. It is known that serum gastrin does not increase in response to secretin or glucagon in some patients with gastrinoma. Thompson et al.[14] reported that serum gastrin in response to i.v. glucagon was not consistently increased, although i.v. injection of glucagon evoked paradoxical increases in serum gastrin levels in all patients in our present and previous case series.[8] Secretin sometimes induces false negative increases in serum gastrin: Pancreatic juice stimulated by secretin regurgitates into the gastric antrum and stimulates the release of gastrin. As glucagon can tend to inhibit pancreatic secretion, glucagon is not likely to evoke this false negative response.

It could be argued that administration of glucagon should be avoided in diabetic patients because glucagon induces hyperglycemia. However, we believe that this effect of glucagon can be ignored, as the hyperglycemic effect is transient.

Conclusion

I.v. and i.a. glucagon provocative tests are useful for diagnosis, tumor localization, and treatment of patients with ZES. Glucagon appears to be a suitable alternative to secretin, which is difficult to obtain.

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Catastrophic *Clostridium difficile* Enteritis in a Pelvic Pouch Patient: Report of a Case

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Abstract
Introduction In recent years, *Clostridium difficile*-associated infection has emerged as an increasingly problematic entity. More virulent strains have been isolated and new manifestations of the infection have been described.
Purpose The primary aim of this manuscript is to describe what we believe to be the first reported case of devastating *C. difficile* enteritis in a patient with an ileal reservoir.
Conclusion A high index of suspicion is required in the appropriate clinical setting in light of the apparently changing spectrum of *C. difficile* disease.

Keywords *Clostridium difficile* · Pelvic pouch · Enteritis

Introduction

Clostridium difficile infection is the most common cause of nosocomial diarrhea and causes of spectrum of colonic inflammation that can lead to fulminant colitis in severe cases. Small bowel involvement has been considered quite rare and has usually occurred in conjunction with concomitant colonic involvement.[1–4] Instances of isolated *C. difficile* enteritis have been recently reported in patients who had previously undergone colectomy.[5–8] We now describe a case of life-threatening *C. difficile* enteritis in a pelvic pouch patient with an endoscopically normal ileal pouch.

No reprints available.

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Report of a Case

A 48-year-old woman underwent a total proctocolectomy with ileal pouch anal anastomosis for ulcerative colitis in 2003. She achieved a good functional outcome with 4–5 bowel movements per day. She was admitted to an outlying hospital in early 2006 with a small bowel obstruction necessitating laparotomy and resection of several inches of distal jejunum. Postoperatively, she developed an enterocutaneous fistula that failed to respond to conservative measures including home total parenteral nutrition. In late 2006, she underwent another laparotomy at our institution with a limited small bowel resection and anastomosis. Postoperatively, she had a somewhat prolonged ileus, but ultimately appeared to recover satisfactorily. Computed tomographic scanning before discharge was negative for abscess or leak.

She was readmitted to our hospital 3 weeks after this laparotomy with profound diarrhea that rapidly progressed over several hours to lactic acidosis and early multi-organ failure. She was brought urgently to the operating room for exploration; a small amount of clear fluid was found in the peritoneal cavity and the small bowel appeared moderately dilated. There was no evidence of perforation, ischemia, or obstruction. Owing to the small bowel dilatation and hemodynamic instability, the abdomen was left open with a Bogota bag and she was brought to the Intensive Care

Unit. A *C. difficile* titer obtained earlier in the day returned as positive; a gram stain of the peritoneal fluid was negative for bacteria. Flexible endoscopy was performed and revealed an essentially normal pelvic pouch without evidence of inflammation or pseudomembrane (Fig. 1); biopsies revealed only minimal chronic inflammation (pouchitis) histologically. She developed multiple small bowel fistulas postoperatively; small bowel biopsy at the bedside revealed changes consistent with *C. difficile* enteritis (Fig. 2). She was treated with a 14-day course of intravenous metronidazole, 500 mg three times daily.

She ultimately made a satisfactory recovery, but her fistulas have not healed with parenteral nutrition. It is expected that she will ultimately require another major surgical procedure.

Discussion

Clostridium difficile infection classically affects only the colon with symptoms ranging from asymptomatic carriage to diarrhea to pseudomembranous colitis or even fulminant colitis with toxic megacolon and perforation.[9] The jejunum appears to be a reservoir of the organism in selected patients, but small bowel involvement has been considered to be quite uncommon.[10,11]

In recent years, a small number of reports of *C. difficile* enteritis have been published. In most cases, the small bowel involvement has occurred in patients with fulminant *C. difficile* colitis.[1–4] However, a few cases have occurred in patients who have had a previous colectomy.[5–8] The risk factors for *C. difficile* enteritis appear to be similar to those of *C. difficile* colitis including advanced age, hospitalization, antibiotic usage, and previous gastrointestinal surgery. In the patients who have had a previous colectomy, it has been hypothesized that the distal ileal microflora is similar to the colonic environment, predisposing to *C. difficile* infection.[3]

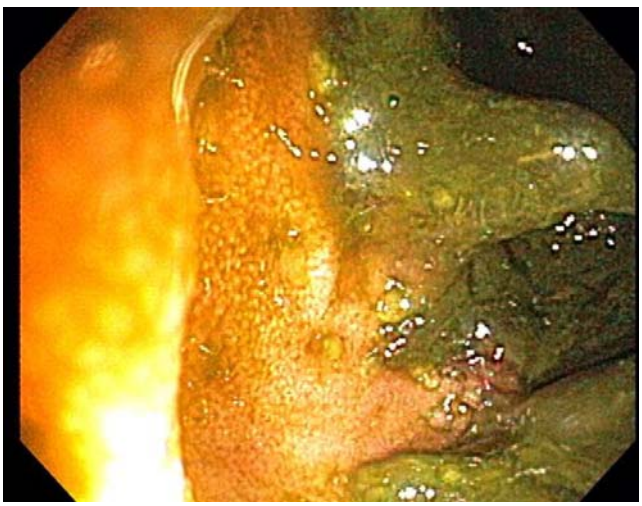

Figure 1 Image of a healthy-appearing pelvic pouch obtained during flexible endoscopy.

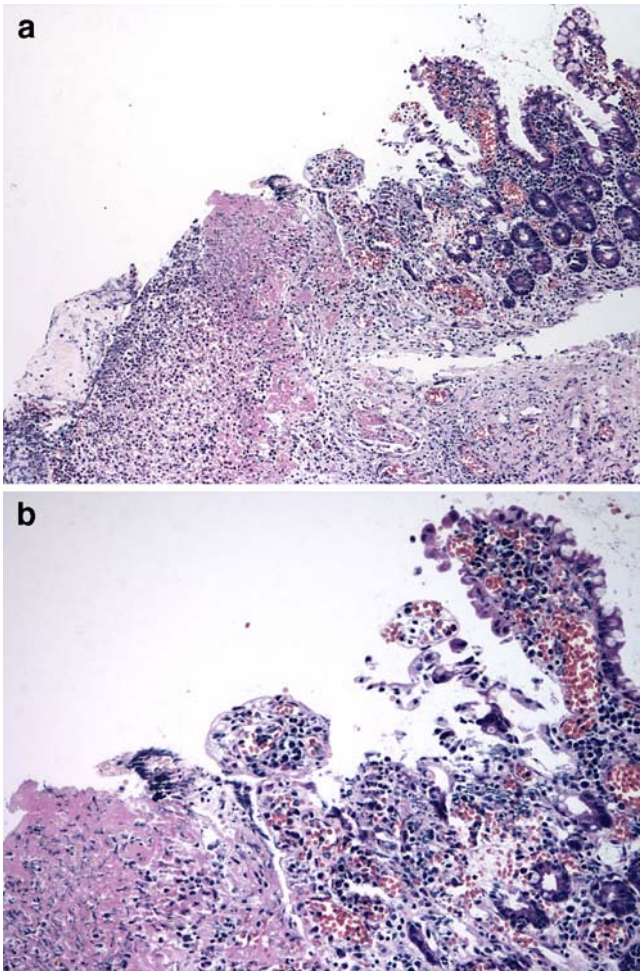

Figure 2 (**a**) A section of the small bowel showing ischemic mucosal ulceration with submucosal edema, inflammation, and hyaline necrosis of submucosal blood vessels (hematoxylin and eosin [H&E] staining, ×100). (**b**) A representative mucosal lesion shows a sharp transition between viable and necrotic mucosa with accompanying inflammation. Classic pseudomembranes are not present, but necroinflammatory exudate covers the mucosal ulcerations (H&E, ×200).

In addition, morphological changes such as colonic-type metaplasia with partial villous atrophy have been described in ileal pouches.[12] *C. difficile* has been reported to be a cause of pouchitis in two patients who had undergone total proctocolectomy with ileal pouch-anal anastomosis.[13,14]

As opposed to *C. difficile* colitis, the outcome of *C. difficile* enteritis has typically been catastrophic, with most affected patients dying. It has been suggested that the increased permeability of the small bowel may result in a more profound illness.[5] This would be very compatible with our patient in that her progression from diarrhea to overwhelming sepsis and multi-organ failure occurred in a startlingly rapid manner. Perhaps most intriguing was the

finding that she developed multiple perforations in the small bowel proximal to her pelvic pouch despite a normal-appearing ileal reservoir. It seems possible that her prior enterocutaneous fistula could have altered her upstream small bowel microflora in such a way that allowed for *C. difficile* overgrowth, similar to what has been reported in cases of enteritis associated with an ileostomy.

It is difficult to determine if this case of *C. difficile* enteritis represents a new manifestation of an old problem or the emergence of a new strain of *C. difficile*. There have been reports of clindamycin-resistant strains of *C. difficile* being responsible for large outbreaks of nosocomial diarrhea in four US hospitals.[15] In addition, *C. difficile* resistance to quinolones has been a concern.[16] Perhaps even more alarming has been the emergence of highly aggressive strains such as the one described in Quebec, Canada.[17,18] Such aggressive strains may be able to affect segments of small intestine that were previously not vulnerable to infection.

Irrespective, it seems evident that the spectrum of *C. difficile* infection is changing and now includes primary small bowel involvement, at least in patients who have undergone colectomy. Consideration of *C. difficile* infection in this setting is required, as *C. difficile* enteritis appears to be a potentially devastating disease with the potential for a rapidly lethal outcome.

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Volume and Outcome for Major Upper GI Surgery in England

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Abstract
Background The correlation between hospital or surgeon volume and outcome for complex surgical procedures has been the subject of several studies in recent years. In the UK, such studies have been used to strengthen the case for centralization of such procedures. The recent availability of easily accessible and fully independent data on hospital outcomes for surgical services in the UK has provided the opportunity to review any potential associations between volume and outcome in the UK.
Methods Hospital Episode Statistic (HES) data were collected through Dr Foster® for four different upper GI procedures (gastrectomy, esophagectomy, pancreaticoduodenectomy, and liver resection) for a 6-year period from 1999 to 2005. Data for each procedure were divided into volume-dependant quartiles to assess any differences in mortality outcome.
Results Generally, mortality rates for all four procedures are lower than previously studies have suggested. A significant trend favoring high volume providers was noted for esophagectomy, with mortality rates varying from 7.8% to 4.0% for lowest to highest volume providers ($p<0.001$). A similar but less clear-cut trend was noted for pancreaticoduodenectomy. There was no significant difference for gastric and liver resection between low- and high-volume providers. There was a 20% decrease in centers performing esophagectomy and 28% for centers performing pancreaticoduodenectomy.
Conclusion There is a volume outcome association for esophagectomy and pancreaticoduodenectomy. There is no association for gastrectomy or hepatectomy.

Keywords Volume · Outcome · Cancer · Surgery

Introduction

The relationship between volume of operations and outcome, in terms of mortality and morbidity, has been examined in many previous studies.[1–5] However, most studies have looked at the association in regions with a distinctly wide variation between high- and low-volume centers, at time periods when mortality rates have been higher than current rates.

Internationally, evidence from these volume outcome studies has been used to support initiatives to centralize cancer services.[6] In the UK, partly as a consequence, this has resulted in the introduction of changes for the provision of upper GI surgical services. The Cancer Outcome Group (COG) guidelines were published in 2001[7] and made recommendations for the further centralization of surgical cancer services for esophageal, gastric, and pancreatic cancers to high-volume hospitals.

These changes have huge implications for health care provision in the United Kingdom. There is, however, very little volume outcome evidence from the UK. The majority of studies are historic and based on data from the United States. These findings may not be applicable to the National Health Service (NHS) in England, where medical services tend to be more evenly distributed compared to other Western countries.

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The aim of this study was to examine English Hospital Episode Statistics to find current mortality rates and to look for evidence of a link between volume of upper GI resection surgery and outcome in terms of 30-day mortality.

Methods

Hospital Episode Statistic (HES)-derived data were obtained from Dr Foster®[1] for all NHS hospitals in England for the following operations: esophagectomy, gastrectomy, liver resection, and pancreaticoduodenectomy. Data were obtained for the time period from April 1999 to March 2005 for each hospital, together with the number of 30-day in-hospital postoperative deaths. The data were arranged into two 3-year cohorts (1999–2002, and 2002–2005) to allow analysis of changes of practice within the timeframe as a result of COG guidelines (Table 1). Emergency operations were excluded.

Statistical Analysis

For each type of resection, hospitals were sorted according to number of procedures performed during the 6-year period, then aggregated into quartiles with similar total caseloads for that procedure. Surgical death rates were calculated for these four groups (Table 2). Hospitals were further aggregated into two groups, and a rate ratio comparing lower vs higher caseload hospitals calculated, with a bootstrap confidence interval using the BCa method and a *P* value using a randomization test (Table 3). These methods appropriately allow for both the marked-over dispersion found in some parts of the data and the small numbers of procedures and deaths in many hospitals.

Results

A total of 159 hospitals in England performed at least one of the operations during the 6 years specified. During this time, there were 8,183 gastrectomies, 8,874 esophagectomies, 3,378 pancreaticoduodenectomies, and 5,672 liver resections.

Table 1 Change in Volume and Mortality from 1999 to 2005

	Number	Mortality (%)	Hospitals
Esophagectomy			
1999–2002	4,529	7.06	134
2002–2005	4,345	4.83	107
Gastrectomy			
1999–2002	4,280	6.3	147
2002–2005	3,903	5.9	145
Pancreaticoduodenectomy			
1999–2002	1,473	6.2	101
2002–2005	1,905	5.7	73
Liver resection			
1999–2002	2,269	2.2	53
2002–2005	3,403	2.6	59

For esophageal resections, the death rate declined steadily from 7.8% among 2,295 cases treated by the 100 hospitals with lowest caseloads to 4.0% among 2,218 cases treated by the eight hospitals with highest caseloads. The 21 higher throughput hospitals had a 46% (95% CI 11% to 95%) lower surgical death rate than the 123 lower throughput ones (P=0.007). Similarly, for the smaller number of pancreatic resections, higher throughput hospitals had a 60% (95% CI 10% to 143%) lower surgical death rate than lower throughput ones, (p=0.016), although the pattern across the four groups is less clearly linear. Conversely, for gastric and hepatic resections, surgical mortality was, if anything, slightly higher among higher caseload hospitals, although with little regular pattern across the four groups (Table 2).

The number of gastrectomies and esophagectomies decreased slightly over the 6 years—decreasing by 9% and 4%, respectively, when comparing the first 3 years with the last. The number of pancreaticoduodenectomy procedures and liver resections increased by 29% and 50%, respectively. Changes over the two time periods showed a mixed pattern. The number of hospitals performing esophagectomy fell from 134 to 107 (20% drop), with the number of units performing less than 10 procedures per year dropping from 90 to 46. A similar picture emerges for pancreatic resection with the number of hospitals performing the operation falling by 28% (101 to 73). The number of liver resections has increased over the two time periods by 50% and consequently the number of hospitals performing hepatic resection has increased from 53 to 59. Gastrectomy volume decreased from 4,280 for the first 3 years to 3,903 for the second period. The number of hospitals performing gastrectomy has not changed significantly (147 to 145).

[1] Dr Foster® (http://www.drfoster.co.uk) is an independent health service research organization, and collates HES data for all NHS hospital-based care in England. Every English NHS hospital must submit HES data for each episode in every patient's hospital stay. This includes diagnoses, coded by ICD-10 (International Statistical Classification of Diseases, 10th revision), and any procedures, coded by OPCS4 (UK Office of Population Censuses and Surveys).

Table 2 Surgical Mortality Rate in the UK by Caseload of Procedures in Quartiles

Resection	Quarter of data	Number of hospitals	Caseload range	Caseload total	Deaths	Death rate %
Esophagectomy	Smallest	100	1–66	2,295	178	7.8
	Small	23	66–122	2,050	131	6.4
	Large	13	132–231	2,311	133	5.8
	Largest	8	235–368	2,218	88	4.0
Pancreaticoduodenectomy	Smallest	80	1–43	907	59	6.5
	Small	13	46–77	810	65	8.0
	Large	8	81–144	781	42	5.4
	Largest	4	173–317	880	33	3.8
Gastrectomy	Smallest	78	1–44	2,029	113	5.6
	Small	39	45–68	2,091	135	6.5
	Large	24	69–100	2,027	115	5.7
	Largest	14	101–244	2,036	137	6.7
Liver resection	Smallest	62	1–197	1,488	46	3.1
	Small	5	211–301	1,307	16	1.2
	Large	4	318–503	1,603	53	3.3
	Largest	2	589–685	1,274	25	2.0

Discussion

This study discloses a mixed relationship between volume and outcome for major upper GI surgery in England. Higher volume hospitals achieved lower 30-day mortality rates for esophageal and pancreatic resections. No volume outcome association was observed for gastric and liver resections. With 26,107 major upper GI operations, this is the largest such cohort studied to date and accurately reflects current practice in England.

Thirty-day mortality rates for esophagectomy showed a steady decline with increasing hospital volume. Previous studies measuring outcome in terms of 30-day[1,15] and in-hospital mortality rates[2,9–14]) found a similar trend, although the effect of volume was larger. An English study[8] examining data from the West Midlands region found there was no difference in outcome after esophagectomy between low-and high-volume hospitals. In our study, the 30-day mortality rate for the smallest English units (7.8%) compares favorably with the previously largest study on esophagectomy where the highest volume units had an in-hospital mortality rate of 8.4%.[2] The significant general improvement in 30-day mortality over the study time period for esophagectomy is encouraging. During this time period, there was a decrease in hospitals performing the procedure by 20% suggesting a process of centralization. However, the 10 highest volume units performing esophagectomy also saw a decrease in mortality rate from 4.3% to 3.4% over the time period. This suggests that, whereas centralization may have made a contribution to mortality rate, improvements in peri-operative care, for example the increasingly widespread use of thoracic epidural, dedicated anesthetic teams and high dependency units, and the introduction of a multidisciplinary approach to esophageal cancer management may have had an equal if not greater affect.

Table 3 Surgical Mortality Rate by Caseload of Trust in Two Groups, with Rate Ratios Comparing Death Rates in Trusts with Smaller vs. Larger Caseloads

Resection	Half of data	Caseload total	Deaths	Death rate %	Rate ratio	95% confidence interval	*P* value
Esophagus	Smaller	4,345	309	7.1	1.46	1.12 to 1.95	0.007
	Larger	4,529	221	4.9			
	Total	8,874	530	6.0			
Stomach	Smaller	4,120	248	6.0	0.97	0.80 to 1.19	0.77
	Larger	4,063	252	6.2			
	Total	8,183	500	6.1			
Pancreas	Smaller	1,717	124	7.2	1.60	1.10 to 2.41	0.016
	Larger	1,661	75	4.5			
	Total	3,378	199	5.9			
Liver	Smaller	2,795	62	2.2	0.82	0.50 to 1.67	0.51
	Larger	2,877	78	2.7			
	Total	5,672	140	2.5			

There was a small but significant volume outcome effect for pancreaticoduodenectomy in this study. All previous studies showed a reduction in 30-day[1,15] and in-hospital mortality rates[2,9–11,16–22] in high-volume hospitals,[2,9–11,16–22] although this was not statistically significant in a recent study from Taiwan.[14]

No evidence for a volume outcome effect for gastrectomy or liver resection was found. Previous studies on gastrectomies, have shown a reduction in 30-day[24]) and in-hospital mortality rates[2,4,10,11,14] for higher volume hospitals. In two studies, the decrease in 30-day[23]and in-hospital mortality[9] was not statistically significant. The few studies that have examined volume outcome for liver resections all demonstrate a very strong volume outcome effect,[1,10,11,25,26] with differences in in-hospital mortality between high- and low-volume centers ranging from 5.6%[11] to 16.6%.[10] The more uniform provision of surgical services in the UK and the lack of "low"-volume centers as defined in previously published data may explain why no association between volume and outcome was observed for gastrectomy and liver resection; and a much smaller effect was seen for esophagectomy and pancreaticoduodenectomy. In addition, patient populations at high- and low-volume hospitals may differ in US-based studies, and thus influence outcome. Recently, Liu et al.[27] reported that for several surgical procedures including esophageal and pancreatic cancer resection, a disproportionately small number of ethnic minorities and poorly insured patients received care in high-volume hospitals.

Average 30-day mortality rates for esophagectomy (6%), pancreatic resection (5.9%), gastrectomy (6.1%), liver resection (2.5%) are much lower than those previously reported in the literature. Halm et al.[3] observed that the average in-hospital mortality rates for esophagectomy, pancreatic resection, and gastrectomy, were 13.9%, 9.7%, and 10.9%, respectively, based on a literature review. However, the majority of previous studies have used in-hospital mortality as a primary outcome, where we have used 30-day mortality rates. Thirty-day mortality rates underestimate operative mortality, and may contribute to the lower mortality rates observed in this study. Differences in overall 30-day mortality rates could also be attributed to differences in study period. Previous studies used older data (generally between 1984 and 1997), when surgical procedures, anesthetic techniques, and peri-operative care were not as advanced. Emergency procedures were excluded in this study, which would also influence mortality rate.

This retrospective study has a number of limitations. The validity of the findings are dependant on the accuracy of the Dr Foster® HES database, and there have been concerns regarding the completeness and accuracy. However, a systematic review of discharge coding accuracy[28] found coding accuracy on average is high (92%) in the UK, especially for operations. The UK has a unique healthcare system, and findings may not be applicable to other countries. Procedure volume and outcome in terms of 30-day postoperative mortality have been examined in this study. However, other factors such as surgeon volume[29] may be significant in influencing outcome, and further health outcomes (resection rates, morbidity, quality of life, and cancer-specific survival) warrant further investigation.

Despite the limitations, this study reflects current upper GI cancer surgery practice in England, and the findings suggest that previous historical studies examining volume and outcome may no longer be relevant to today's surgical environment. There is clear evidence of better outcomes in terms of postoperative mortality in high-volume centers when resecting esophageal and pancreatic cancers, and this justifies the centralization of services for these cancers. However, evidence for gastric and liver resections is less clear, and our findings do not endorse a drive to centralize surgery for these cancers.

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A Better Method for Preventing Infection of Percutaneous Endoscopic Gastrostomy

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Abstract
Background Percutaneous endoscopic gastrostomy (PEG) has been widely used to maintain enteral nutrition in dysphagic patients. Local and occasional life-threatening systemic infections are still the most common complications, and the major infection source may be nosocomial flora. The effect of antibiotic prophylaxis on reducing peristomal infection is popularly accepted. However, it is accompanied with a possible risk of increasing antibiotic resistance.
Aim This study attempted to determine whether 14-day discharge before PEG could reduce the rate of peristomal infection.
Materials and Methods Fifty patients who had received PEG in our hospital were included in this study and followed for at least 6 months (except for those patients who died during this period). Patients were separated into two groups randomly. Twenty-five patients received PEG during in-hospitalization (group A). The other 25 patients received PEG until discharge at least for 14 days (group B). The most frequent indication for PEG insertion was the neurological condition. Risk factors for peristomal infection were analyzed statistically using logistic regression and expressed by odds ratios. Every possible factor was analyzed by chi-square test or Student's *t* test.

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Result Our data showed that group A had a higher peristomal infection rate than group B (32 vs 8%) ($p<0.05$).Group A also showed more need of antibiotics. The risk factors related to peristomal infection were group A and lower albumin. The total rate of 30-day mortality was 4%.
Discussion When compared with previous data, our study showed a similar infection rate in group A, a lower infection rate in group B, and a lower 30-day mortality rate. This meant that one period of discharge could reduce the peristomal infections caused by colonized bacteria. It also decreased the need of using antibiotics and might avoid the possible adverse consequence of promoting bacterial resistance, which is an alarming and growing problem in hospital practice.
Conclusion We suggest that a 14-day grace period after discharge, before PEG insertion, may decrease peristomal infection rate, length of hospital stay after PEG, and the need for antibiotics. This is suitable for moral and ethical considerations.

Keyword Percutaneous endoscopic gastrostomy

Introduction

Since percutaneous endoscopic gastrostomy (PEG) was introduced to clinical practice by Gauderer et al. in the 1980s,[1] it has been widely used to maintain enteral nutrition in dysphagic patients of cerebrovascular disease, oropharyngeal malignancy,[2,3] and motor neuron disease.[4] It is safe due to low procedural mortality. Nevertheless, local and occasional life-threatening systemic infection is still the most common complication. Previous studies have reported overall rates of peristomal infection ranging from 4 to 60%.[5–7] Several investigators have reported low rates of wound infection in patients who were already receiving antibiotics at the time of PEG;[8,9] some centers routinely use antibiotic prophylaxis.[10] However, not all evidence supports routine prophylaxis, particularly in patients with 'benign' disease indications for PEG insertion. Conflicting results, however, have been obtained in prospective clinical trials of antibiotic prophylaxis in PEG.[11,12] Besides this, antibiotic prophylaxis may bring a possible adverse sequence of promoting bacterial resistance.

The nosocomial colonization of bacteria is an important source of procedure-related infection.[13,14] A previous study using univariate and multivariate analysis found that in-hospital insertion of PEG was a predictive factor for mortality.[15] In another previous retrospective study, ambulatory patients were found to survive longer after PEG insertion than hospitalized patients.[16] However, there are few papers discussing the relationship between peristomal infection and hospitalization.

The purpose of this prospective study was to survey the impact of 14-day discharge on the peristomal infection of patients in whom we attempted a PEG (PEG). We also surveyed the indications, success rate, procedure-related complications, and long-term outcome.

Materials and Methods

Fifty patients included in our study had received PEG in Kaohsiung Municipal Hsiao Kang Hospital from Oct. 2003 to Aug. 2005. Follow-up continued until death or Mar. 2006. In the beginning, we separated these patients into two groups randomly. Twenty-five patients received PEG during in-hospitalization when they met the indication of PEG (group A). The other 25 patients were discharged when they were stable and met the indication of PEG, and then they received PEG 14 days after discharge (group B). The most frequent indication for PEG insertion was the neurological condition, the commonest being stroke. A gastroenterologist confirmed suitability for gastrostomy. Exclusion criteria were as follows: a contraindication to PEG, treatment with any antibiotic within the past 4 days, neutropenia (<500 cells/dl), or serum creatinine concentration >300 mmol/l. Written informed consent was required, and the ethics board of Kaohsiung Municipal Hsiao Kang Hospital approved this study.

The use of an antiseptic mouthwash was routinely given before PEG. All patients received parenteral antibiotics against Gram-positive organisms 30–60 min before the procedure. The pull-type PEG procedure with a 20-Fr PEG tube (Wilson-Cook, Medical GI Endoscopy) was performed for all patients. Xylocaine throat spray was used for anaesthesia and intravenous midazolam administered for sedation. The initial dressing (without local antiseptics) was performed by a nurse and daily dressing changes (with beta-iodine only) were standardized and performed by family members throughout the observation period. The enteral feeding started 4 h after PEG tube placement. Complications and post-procedure infections were recorded. All patients were followed for at least 7 days. Blood cell counts were done on days 1, 4, and 7 after gastrostomy. Monitoring included the measurement of body temperature three times daily, recording of peritoneal irritation and abdominal pain, and assessment of potential adverse events and clinical complications.

Peristomal infection endpoints End points were documented on post-intervention days 1, 4, and 7. Local infection was scored using a modified Jain et al. scale:[8] erythematic diameter (0=absent, 1=<0.5 cm, 2=0.5–1.0 cm, 3=>1 cm); exudation (0=absent, 1=slight, 2=dressing damp, 3=dressing soaked); and purulent secretion. An aggregate score of 0.3 or the presence of pus was classified as local infection.

This simplified scale was supported by previous studies showing purulent discharge to be the decisive factor in assessing local infection in almost 100% of cases.[8,9] When purulent secretion was suspected, we collected material for microscopy and culture. Systemic infections included pneumonia (demonstrated by x-ray), signs of sepsis (positive blood culture, hyper- or hypothermia, hyperventilation, tachycardia, leukopenia, or leukocytosis), peritonitis (local peritonitis and signs of systemic infection), and urinary tract infection (UTI; bacteriuria). Post-intervention antibiotic therapy for peristomal or systemic infections was also recorded.

Statistic analysis Risk factors for peristomal infection were analyzed statistically by using logistic regression and expressed by odds ratios (OR). Categorical data were compared by using the chi-square test, and the Student's *t* test was used to compare the means of normally distributed continuous variables. OR are expressed with 95% confidence intervals; a $p<0.05$ was considered significant.

Result

The two groups were similar in patient characteristics, indications for PEG, and possible infection risk factors, e.g., diabetes and obesity (body mass index; Table 1). The rates of using histamine receptor type 2 (H-2) blockers or proton pump inhibitors in group A (hospitalized patients) and group B (outpatients) were 80% (20/25) and 76% (19/25), respectively. There was no significant difference between two groups($p>0.05$). The indications for PEG were neurologic disorders ($n=44$, 88%), malignancy ($n=4$, 8%), and motor neuron disease ($n=2$, 4%). All of these patients were fed with nasogastric feeding tubes before receiving PEG. PEG was successfully placed in all of the 50 patients. There were no obvious hemorrhages, perforations, or fatal complications during the procedure, nor was there any procedure-related mortality. The mean observing period was 8.12 days (8.12±2.1 days) in the in-hospital (group A) patients, 8.03 days (8.03±1.7 days) in the discharged (group B) patients, and 8.07 days (8.07± 2.0 days) overall.

Table 1 Patient Characteristics

	Group A	Group B
Male:female	16:9	15:10
Age	67.84±11.32*	66.36±11.9*
Albumin	2.85±0.25*	2.81±2.09*
BMI	21.04±1.76*	21.15±2.09*
DM (%)	28%	24%

BMI Body weight index, *DM* diabetes mellitus
*All the data were expressed as mean±SD.

Rates of infections The rate of peristomal infection was 20 vs 4% up to day 3 (group A vs group B), 32 vs 8% up to day 7 ($p=0.019$), respectively (Fig. 1). The presence of pus was correlated with a score 3 in 87.5% of patients with local infection. Of the local infections, 60% occurred in the first 72 h (6/10). One patient in group A had oxacillin-resistant *Staphylococcus aureus* infections.

The systemic infections occurred in three patients (12 %) of group A and two patients (8 %) of group B ($p>0.05$; Fig. 1). Two cases of pneumonia, two of urinary tract infection, and one of acute bronchitis were observed, three of which had comorbidity of DM. Two patients developed sepsis that was associated with pneumonia. Peritonitis did not occur in either group.

Risk factors related with infections Patients with the following risk factors identified between admission and PEG also had an increased risk of peristomal infection: group A (OR=79.213), serum albumin concentration less than 2.8 g/dl (OR=156.23).

Post-intervention antibiotic therapy Intravenous antibiotic therapies were administered to eight of group A and two of group B patients (40 vs 8%, respectively; $p<0.05$) after PEG (Fig. 2). The rates of antibiotics for systemic infection, peristomal infection, and combined infections were 20, 60, and 20%, respectively.

Mortality One of group A (4%) and one of group B (4%) died during the following period (total mortality 4%). Both patients died of pneumonia with sepsis within 30 days after PEG. These two patients also showed peristomal infection. Both had lower albumin levels but only one had DM.

Discussion

Our experience suggested that PEG is safe and has a low complication rate, even in patients with multiple medical problems. In our study, the risk factors related with peristomal infection were group A, lower albumin (<2.8 g/dl). It might be associated with colonized flora during long-term admission. The infection rate was higher in group A (32%) in this study. However, it was similar to a previous study's data,[8] so we did not have a higher infection rate compared to other studies. The infection rate reduced significantly in group B (8%). This meant that one period of discharge could reduce the infection rate after PEG.

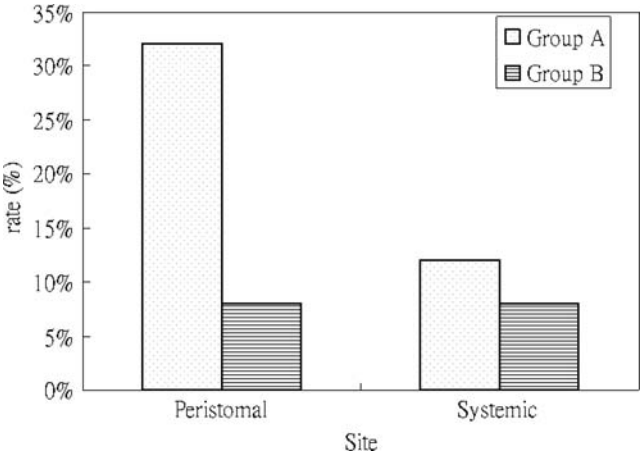

Figure 1 Infection rate of both groups. The peristomal infection rates in groups A and B were 32 and 8%, respectively ($p<0.05$). The systemic infection rates in groups A and B were 12 and 8%, respectively ($p>0.05$).

On the other hand, it might also be related to our standard post-intervention care. We tried to decrease the length of hospital stay by teaching the family how to change the wound dressing since 1 day after PEG. This might have lead to higher possibility of wound contamination. Besides these, earlier feeding timing (4 h after PEG) in our protocol might also be related to peristomal infection.

Patients who had sterile cultures and required no medical or surgical treatment may have had inflammatory reactions associated with foreign material rather than true infection. Such minor or presumed wound infections occurred with a similar frequency among patient group A (5of 25, 20%) and group B (4 of 25, 16%; $p>0.05$).

Our study showed a lower mortality rate of 4% during 30 days after PEG. This compared well with previous studies[5,7] but might be related to the fact that we excluded patients with acute illness that was a risk factor of mortality.[16–18] The previous studies showed that higher 30-day mortality rates were attributed to a trend for less strict patient selection over the last few years.[19,20] Ten years ago, more than 80% of PEGs were placed in patients with cardiovascular disease, motor neurone disease, ear–nose–throat tumors, or multiple sclerosis. This proportion fell to 69% in the current series, due to an increase in PEG placement for acute medical conditions where the long-term benefits of PEG are unproven. In our opinion, PEG tubes should not be placed in the acute care setting, when feedings can be given via nasogastric tubes. Moreover, it should be delayed until the patient's acute illness has resolved; a previous study has also supported this opinion.[16]

In the largest study to date, Grant et al.[21] retrospectively reviewed 81,000 American Medicare beneficiaries who underwent PEG. They showed a 30-day mortality rate of 25%. They found that 30-day mortality was highest among those with non-aspiration pneumonia. Others have found that aspiration pneumonia was a risk factor for 30-day mortality.[22] Other previous studies revealed that factors such as old age (>75 years), previous aspiration pneumonia, urinary tract infection, dementia, long-term hospitalization, malignancy, and lower body mass index increased the risk of mortality.[22–25] Hypoalbuminemia (albumin <2.8 g/dl) was also a risk factor.[26,27] In our study, the major cause of mortality was pneumonia only, where the underlying disease was cerebrovascular disease and both patients had comorbidity with DM. This finding was similar to previous studies.[11,28]

Wound infection at the gastrostomy site may be due to the pull technique because the wound is mainly contaminated by Gram-negative bacteria originating from the oropharynx.[11,29] In the last 2 years, the first five colonized bacteria from wounds in our hospital were *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus* spp., and oxacillin-resistant *Staphylococcus aureus*, in order. In our study, we found the major two bacteria identified from group A were *P. aeruginosa* and *E. coli*. It may be regarded as colonized flora due to long-term hospitalization. On the other hand, the bacteria identified from group B were *S. aureus*. It was not related to the colonized bacteria in our hospital.

Antibiotic treatment may have an effect on the incidence of infection but not on the length of hospital stay in patients receiving PEG.[30] However, the potential benefit of increasing in-hospital use of antibiotics should be weighed against the possible adverse consequence of promoting bacterial resistance, which is an alarming and growing problem in hospital practice. Because gastrostomy placement can damage normal innate defense mechanisms in the upper gut resulting in bacterial overgrowth, various bacteria were identified from exudates taken from patients with wound infections with a preponderance of upper respiratory tract organisms.[30] Accordingly, we routinely used an antiseptic mouthwash before PEG. Our data showed that we did not

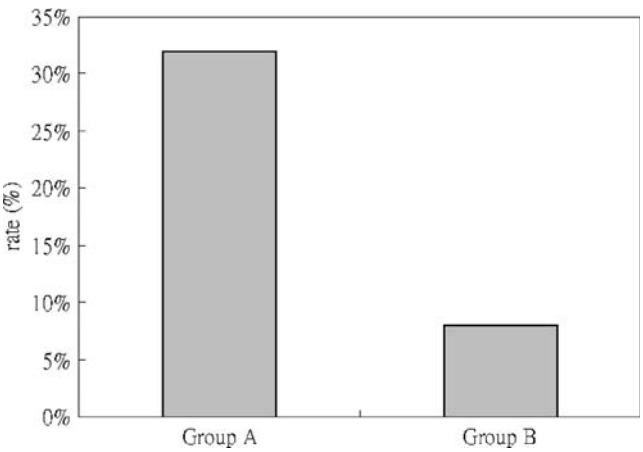

Figure 2 Rate of patients treated with antibiotics. The rate of antibiotics used in groups A and B were 40 and 8%, respectively ($p<0.05$).

meet higher infection rates than the others' data, even in group A. According to this finding, we thought that the routine use of an antiseptic mouthwash before PEG might have some effect on preventing patients from infection and would not have the possible disadvantage of promoting bacterial resistance. However, we should point out that this procedure must be carried out carefully because of swallowing dysfunction and the attendant risk of aspiration in these patients. Regardless, we also support routine antibiotic prophylaxis before PEG for high risk patients, which is in broad agreement with current recommendations.[31]

As we know, the half-life of albumin is about 21 days; therefore, we decided the optimal discharging period was 14 days. In our study, we found that the albumin levels were similar in both groups. It showed that the discharging period did not influence the nutrition status. However , it is needed to survey the optimal period out of hospital before PEG in further study.

For the above reasons and for moral and ethical considerations,[32,33] we suggest that a 14-day grace period after discharge, before PEG insertion, may decrease peristomal infection rate and the need of antibiotics. It also relatively shortens the length of hospital stay after PEG.

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Intrahepatic Repair of Bile Duct Injuries. A Comparative Study

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Abstract
Introduction The frequency of bile duct injuries associated to cholecystectomy remains constant (0.3–0.6%). A multidisciplinary approach (endoscopical, radiological, and surgical) is necessary to optimize the outcome of the patient. Surgery is indicated when complete section of the duct is identified (Strasberg's E injuries) requiring a bilioenteric anastomosis as treatment. Nowadays, the most frequent technique used for reconstruction is a Roux-en-Y hepatojejunostomy. Long-term results of reconstruction are related to several technical and anatomic factors, but an ischemic duct (with subsequent scarring) plays a mayor role. In this paper, we report the results of biliary reconstructions comparing the extrahepatic—probably ischemic—to intrahepatic—non ischemic—repairs.
Methods We reviewed the files of patients referred to our hospital (third-level teaching hospital) for bile duct repair after iatrogenic injury from 1990 to July 2006. Injury classification, time lapse since injury, surgical repair technique, and long-term follow-up were noted. In all cases, a Roux-en-Y hepatojejunostomy was done. Partial resection of segment IV was performed in 136 patients to obtain noninflamed, nonscarred, nonischemic biliary ducts with the purpose of reaching the confluence and achieving a high-quality bilioenteric anastomosis. An anastomosis at the level of the confluence was attempted in 293 patients (in 198 the confluence was preserved and in 95 it was lost). In the remaining 80 patients, a low bilioenteric anastomosis was done at the level of the common hepatic duct. We compared intrahepatic (198) and extrahepatic (80) repairs.
Results A total of 405 cases (88 males, 317 females) were identified, with a mean age of 42 years (range 17–75). All of the injuries were classified as Strasberg E1, E2, E3, E5 (less frequent); those with E4 classification (separated ducts) were excluded. In all cases, the confluence was preserved (N=293). Thirty-two cases were repaired minutes to hours after the injury occurred. The remaining 373 patients arrived weeks after the injury. In 198 cases, an intrahepatic repair was done, including the 136 in which resection of segments IV and V was part of the surgery. In the remaining 80 cases (operated between 1990 and 1997), an extrahepatic repair was done at the level of the common hepatic duct where the surgeon found a healthy duct. Twelve (15%) of the 80 cases with extrahepatic anastomosis required a new intervention (surgical or radiological), compared to only 8 of the 198 (3%) that had an intrahepatic anastomosis (P=0.00062). Good results were obtained in 85% and 97% of the cases with extrahepatic anastomosis and intrahepatic anastomosis, respectively. Both groups had a reintervention rate of 7% (20/278).
Conclusions An intrahepatic anastomosis requires finding nonscarred, nonischemic ducts, thus allowing a safe and high-quality anastomosis with significantly better results when compared to the low-level anastomosis group.

Keywords Bile duct · Injury

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Introduction

Laparoscopic cholecystectomy was introduced two decades ago; currently it has a diversity of indications and is frequently performed; thus, iatrogenic bile duct injuries still remain constant.[1] Patients require a multidisciplinary approach (endoscopical, radiological, and surgical), and surgery is indicated in cases in which complete section of

the duct is shown.[2] Several technical and anatomical factors have a direct effect on the long-term results of biliary reconstruction. Duct quality, essential for a successful reconstruction, depends on circulatory status and fibrosis and/or inflammatory reaction.[3,4] The circulatory status of the duct is difficult to evaluate. When the repair is attempted at the index surgery (when the injury occurred), the level of ischemia is difficult to assess and in some instances interruption of the right hepatic artery is also shown. The higher the injury, the higher the probability of right hepatic injury.[5]

After the injury, extrahepatic bile ducts are jeopardized by ischemia. Circulatory status is more difficult to assess when repair is attempted several days after injury.[6] Several authors have emphasized the necessity of delaying surgical repair until hilar inflammatory reaction has subsided and all ischemic damage has occurred.[7] We have shown better results with intrahepatic repair (IR) in the acute status of the injury (at the index operation) compared to the extrahepatic repair.[8] In this paper, we report the long-term results of a comparative study between those patients who had an intrahepatic repair and those with an extrahepatic one.

Methods

We reviewed the files of patients referred to our hospital (third-level teaching hospital) for bile duct repair after iatrogenic injury from 1990 to July 2006. Injury classification, time lapse since injury, surgical repair technique and long-term follow-up were noted. The files of the patients with surgical repair were reviewed and a comparative study was done between the patients who had an intrahepatic Roux-en-Y hepatojejunostomy and those with an extrahepatic one. The surgical referral note was reviewed (when available and trustworthy) and ultrasound, magnetic resonance imaging (MRI), computed axial tomography (CAT) scan, endoscopic retrograde cholangio pancreatography (ERCP), fistulography, and, infrequently, percutaneous cholangiography were used to outline biliary anatomy and classify the injury. Percutaneous cholangiography was performed in patients with cholangitis that required bile duct drainage. Patients in which the confluence was lost (N=80) were excluded from this study.

Long-term results were evaluated according to Lillemoe's criteria.[14] Adequate results were defined as postoperative normal direct bilirubin levels and absence of cholangitis. Inadequate results were considered when the patient had abnormal liver function tests, cholangitis, and subsequent radiological and/or surgical reinterventions.

Our diagnostic approach was tailored to each patient's condition.[6] An endoscopic and/or radiological approach was preferred if continuity of the bile ducts was found, and the possibility of dilation of the bilioenteric anastomosis dilation was evaluated if there were previous repair attempts.

An elective Roux-en-Y hepatojejunostomy was performed in all patients that were surgically repaired. Briefly, after liberating adhesions of the right upper quadrant, careful inspection of colon, duodenum, jejunum, and ileum was done to rule out the presence of fistulas. Most were managed by simple closure, with or without omental or serosal patch; the remaining required resection of the involved viscus. As we have found some cases in which the Roux-en-Y had been erroneously constructed or placed,[9] the Roux-en-Y limb was carefully inspected, especially when the patient had a previous repair attempt; if required, another defuctionalized limb was created. Then, we dissected the liver hilus plate and identified the hepatic artery. All attempts were made to preserve the branches of the hepatic artery so as to minimize ischemic damage of the intrahepatic ducts. Bilioenteric anastomosis was done with interrupted monofilament absorbable stitches when the main lumen of a duct was healthy (i.e., adequate circulatory status without macroscopic fibrosis and/or inflammatory reaction), according to our earlier experience.

The placement of a stent was decided according to the anatomic status of the duct.[10] After our initial protocol, which showed that an intrahepatic approach had better results in acute injuries, we decided to change to intrahepatic anastomosis in all electively operated patients. Briefly, we routinely remove the base of segments IV[11] and V[12] (Fig. 1). In some cases, only the edge of the segments is removed, whereas in others a 2×3 cm wedge is removed to expose the anterior aspect of the ducts. Small amounts of bleeding are controlled by compression. After careful exploration of the duct with a small Bakes dilator, the anterior aspect of the duct is completely dissected to the confluence level, and the dilator is directed to the left duct and to the anterior opening. The lateral and posterior aspects of the ducts are not dissected. We prefer fine (5-0) stitches in small bleeding vessels that cross over the ducts rather than electrofulguration. Next, a latero-lateral anasto-

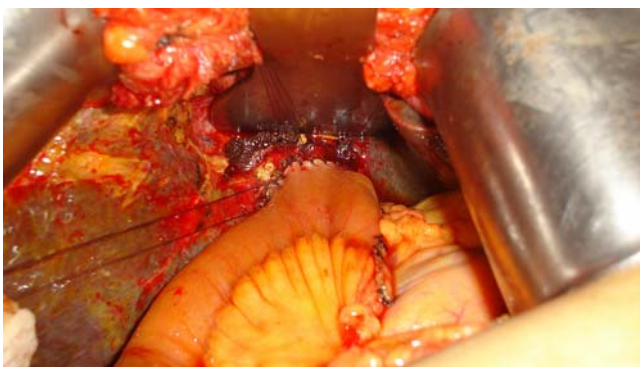

Figure 1 Intraoperative view of the hepatic hilus after partial segment IV resection and jejunal limb placement.

mosis is done to the jejunum with isolated everted stitches of absorbable monofilament. The anastomosis starts at the level were the healthy duct is found. This approach is an excellent choice for small thin ducts.[13]

As a result of this technique we have a wide, tension-free, nonischemic anastomosis for all types of ducts and injuries.

Results

From 1990 to July 2006, a total of 405 patients were surgically treated at our hospital for bile duct repair after iatrogenic injury. Mean age for the whole group was 42 years (range 17–75). All injuries were classified as Strasberg E (all subtypes, excluding E-4 cases—separated ducts).

Thirty-two cases were repaired minutes to hours after the injury. The remaining 373 arrived days or weeks after the injury with heterogeneous symptoms and findings including intraabdominal collections, external and internal biliary fistulas and occluded ducts, and/or anastomosis. Surgical treatment was done when either the radiological or endoscopical approach was inadvisable and when the patient's general condition allowed the surgical procedure.

In 293 cases, the confluence was preserved. In all cases, elective Roux-en-Y hepatojejunostomies with 198 intrahepatic (IR) and 80 extrahepatic repairs (ER) were performed achieving a wide, tension-free high-quality bilioenteric anastomosis. The same surgical technique was used in all cases.

Mortality was 0.7% in the IR group. This corresponded to a patient with Von Giercke disease with a very large liver and severe portal hypertension that developed a postoperative refractory lactic acidosis. On the second postoperative day, the patient required reoperation and presented a massive bilioperitoneum with ascites. No mortality was recorded in the ER group. None of the morbidity or mortality registered was directly attributed to the removal of segment IV.

Five cases (3%) from the IR group were classified as having inadequate results as they required subsequent radiological and/or surgical interventions. Twelve patients from the ER group (15%) were classified as failures (P= 0.00062). Mean follow-up was 64 months (range 12–180 months). Good results were obtained in 97% of the IR group compared to 80% of ER one. Of the 293 cases, 8% were lost in follow-up (total 26 cases, 18 in the IR group, and eight in the ER group).

Both groups presented minor nonsignificant postoperative complications (wound seroma and infection, 8% for both groups, intraabdominal collections that were percutaneously drained in 3%).

An external biliary fistula was registered in 26 cases (9%): eight patients in the ER group and 18 in the IR group. In all cases, a peritoneal subhepatic silastic drain was placed and the fistula disappeared in a mean of 5 days (range 3–20). No further therapeutic maneuver was required.

Three cases from the ER group presented late mortality. They developed liver cirrhosis and portal hypertension with subsequent hepatic failure (46th and 80th month after surgery). Two are on the waiting list for liver transplant and the third died after removal of the left lateral lobe (25th postoperative day) because of persistent cholangitis. She was operated 2 years after the initial repair and died of liver failure and hepatorenal syndrome.

Six patients of the ER group had a second surgery in which a intrahepatic repair was attempted. In four patients, it was possible to do a HIR and in two, a portoenterostomy with transhepatic stents was done. One of these patients developed liver cirrhosis and is on the waiting list for liver transplant. The remaining patient has evolved adequately with frequent transhepatic stent changes.

Two patients from the IR group needed reoperations. Both were treated with transhepatic stents and a portoenterostomy. They have evolved adequately with frequent transhepatic stent changes (every 4–6 months). The cholangitis of the remaining three patients considered as failures was medically treated. All required removal of the right lobe because of persistent cholangitis and segmentary liver involvement.

Discussion

Our findings show that in our hands, an intrahepatic repair of biliary injuries has better results compared to an extrahepatic repair, and we consider it to be the best alternative for most patients. These require treatment at a tertiary care center as a multidisciplinary approach is needed to repair complex biliary injuries. Complex injuries,[15] as described by Walsh, are those that require a bilioenteric anastomosis with an individualized approach; a surgical repair is indicated when loss of substance and continuity of the ducts is found, as in Strasberg E injuries.

Most injuries in laparoscopic cholecystectomy are a combination of section and ablation of the duct as a result of the type of dissection done in the procedure, in which electrofulguration (and sometimes clip placement) interrupts anatomical circulation in the lateral aspect of the duct.

Among the different types of bilioenteric anastomosis, the Roux-en-Y hepatojejunostomy offers the best choice. Defunctionalized limbs guarantee the absence of intestinal reflux into the bile ducts. Some fibers that are present in the intestinal lumen can promote transitory dysfunction of the anastomosis. Bile colonization (not precluded completely by the Roux-en-Y limb) promotes development of sludge and stones that can increase the transitory dysfunction and contribute to an inflammatory reaction

secondary to the obstruction that eventually leads to occlusion of the anastomosis.

Hepatoduodenal anastomosis has also been used to repair this type of injuries. However, this approach results in a tense anastomosis, as the liver returns to its normal position in spite of the wide Kocher maneuver, which is used to ride the duodenum up to the liver hilus. Another problem is that macroscopic food reflux (not only intestinal contents) can be found in the biliary tree. When fistulization of this type of anastomoses occurs, the patient usually has a high-volume fistula, impaired oral feeding, and systemic inflammatory reaction. Nevertheless, some very well selected cases can be managed using this approach.

One of the main causes of dehiscence and/or stenosis (the first appearing in the early postoperative period and the latter in the postoperative period) results from ischemic damage of the ducts. Ischemic ducts are very difficult to assess. In these injuries, the circulatory status of the duct is difficult to evaluate. Right hepatic artery damage has been documented in complex injuries (the higher the injury, the higher the probability) and the consequence of this type of injury is heterogeneous.[16]

Some of these cases have hepatic necrosis with hepatic abscess. Others show intrahepatic stenosis of the ducts that produces cholangitis, some of which are refractory to medical and radiological treatment and will require a hepatectomy (Mercado et al. 2007, submitted).

In many circumstances, even with intact right and left hepatic arteries, ischemic damage of the ducts still occurs. This is mainly the consequence of devascularization of the duct that is being retracted laterally and the softening of the vessels from the lateral aspects of the ducts caused by electrofulguration. When the patient has a history of a previous repair attempt and a stenosis of the bilioenteric anastomosis, we expect to find a fibrous, scarred, and retracted duct. If a new anastomosis is attempted at this level, the probability of failure is higher.

As the ischemic status of the duct cannot be evaluated days after the injury, several authors have proposed the placement of a transhepatic catheter to drain the ducts, divert the bile flow, thus diminishing the inflammatory reaction and allowing the injury to stabilize, so that electively, a high-quality bilioenteric anastomosis can be done.[17]

A high intrahepatic repair warrants a high-quality bilioenteric anastomosis. A bilioenteric anastomosis should be tension-free, as wide as possible, done in ducts without scars and/or ischemic, and/or inflammatory reaction. A defunctionalized limb prevents reflux of intestinal contents.[18]

After sectioning the hilar plate, in one third of the cases, we will find healthy ducts. Dissecting the anterior aspect of the ducts only guarantees the attainment of a non-ischemic duct. In the remaining 2/3 of the cases, partial removal of the base of segments IV and V is an easy and well-tolerated maneuver that allows us to obtain healthy ducts and also gives us room to place the limb and obtain a tension-free anastomosis.

The parenchyma is transected minutes after sectioning the hilar plate. We have recorded no morbidity and mortality attributed to removal of the liver; subhepatic collections are usually related to leaks of the anastomosis, but not to resection of small amounts of liver.

Absorbable, fine (5-0) monofilaments, hydrolysable sutures, allow an adequate apposition of the epithelium to the mucosa with a diminished inflammatory reaction. Inflammatory reactions produce subsequent scarring and/or dehiscence and leaks. Patients with leaks also have a perianastomotic reaction that can result in late stenosis. Low-volume fistulas and subhepatic collections are treated conservatively with a percutaneous drainage.

Separate ducts represent a challenge. In a few instances, the confluence is lost as a direct consequence of section or ablation at the index operation. This is particularly true in patients with a low extrahepatic confluence.[19]

Stones, sludge, and bile debris are the consequences of stasis and secondary colonization of the bile. In some cases, only isolated stones are found with normal bile; other patients have a large amount of pigmented stones that can be easily removed and some have completely abnormal bile with only sludge and casts of bile in their ducts. The development of this latter type of bile is unpredictable. In our experience, this finding is also associated with an unfavorable outcome. These cases have a higher incidence of postoperative cholangitis and remain with abnormal function tests, despite a patent anastomosis. Deposits of sludge at the level of the anastomosis are more likely to appear with subsequent dysfunction of the anastomosis. It is not clear if the use of oral biliary acids and antibiotics play a role in the prevention of stent obstruction or in correcting bile characteristics.

In other instances, lost of confluence is the consequence of an ischemic duct, bilomas, and/or subhepatic abscesses. Strasberg E-3 and E-4 types of injury sometimes require a double-barrel anastomosis or a portoenterostomy with transhepatic drains.[20] This type of injury has a bad long-term prognosis. In our experience, one third of these patients require radiological or surgical reintervention.

Performing an IR in these patients allows a wide anastomosis to the left duct, with inclusion of the right duct. If the right duct is isolated, several other approaches can be done. Strasberg has described a technique in which partial removal of segment V allows the exposure of the duct, permitting a safe anastomosis.[12] The IR is proposed for those cases in which the injury is near the confluence and where a simple anastomosis is difficult. We have used this technique for thin ducts ("the bile duct growing factor"), showing that it is an excellent alternative for repair.[13]

It can be argued that if an intrahepatic repair is done routinely, the "safe net" for subsequent repair is lost. We believe that this approach has a low failure rate and that reoperation is required in very few instances. An intrahepatic anastomosis assures a nonscarred, nonischemic duct to allow a safe and high-quality anastomosis with significantly better results compared to the low-level anastomosis group.

Ideally, a prospective, controlled, randomized trial would be the ultimate scenario to confirm that intrahepatic repairs are better than extrahepatic repairs. However, a study of this nature is hardly feasible since each injury, although classifiable, has its own features and circumstances.

The limitation of our study is a selection bias. Indeed, the two groups were done in different eras. The low repair was done at the beginning of our learning curve, whereas the intrahepatic repair has been performed in the last years. Our increased experience undoubtedly has had a positive impact on our results. We will surely obtain better results when a wide, tension-free anastomosis can be performed on nonischemic, nonsecured ducts.

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Endoscopic Drainage of Pancreatic Pseudocysts

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Abstract Pancreatic pseudocysts arise as a complication of acute and chronic pancreatitis, pancreatic trauma, or after surgery. Endoscopic treatment of pancreatic pseudocysts can be achieved using transpapillary and/or transmural (transgastric or transduodenal) approaches with acceptable success rates, complication rates, and recurrence rates. Advantages of endoscopic drainage is the avoidance of external pancreatic fistula.

Keywords Endoscopic drainage · Pancreatic pseudocysts · Fluid collection

Introduction

Pancreatic pseudocysts arise as a consequence of pancreatic injury, which results in disruption of the pancreatic duct or side branches.[1] Ductal disruption can be caused by acute pancreatic injury (acute pancreatitis, trauma, surgical resection, or injury to the pancreas during abdominal surgery) or chronic injury (chronic pancreatitis, autoimmune pancreatitis). Endoscopic therapy is directed at drainage of the fluid collection using a transmural approach and/or transpapillary approach.

Types of Fluid Collections

Classification systems exist for defining types of pancreatic fluid collections.[1] When undertaking endoscopic therapy of a pseudocyst, however, it is important to make two main distinctions: 1) Is the collection composed primarily of liquid or does it contain significant solid debris? and 2) What is the status and etiology of the disruption of the main pancreatic duct? The approach to collections that are composed primarily of fluid (pseudocysts) is different than that of those containing significant solid debris (organized pancreatic necrosis), as liquefied collections can be managed with either placement of modest-sized diameter stents via transpapillary or transmural approaches alone.

The mechanism of formation of an acute pancreatic pseudocyst is usually as a result of limited necrosis that produces a pancreatic ductal leak. It is important to note that patients with significant pancreatic necrosis may develop a collection that can be mistaken for a pseudocyst by computed tomography (CT). Endoscopic treatment of these collections by typical pseudocyst drainage methods may result in infectious complications because of inadequate removal of solid debris.[1,2]

Chronic pseudocysts arise as a sequela of downstream pancreatic obstruction from fibrotic strictures and/or stones resulting in a pancreatic ductal leak.[3] Infected pancreatic pseudocysts are referred to as pancreatic abscesses in some classification systems.[1]

Indications for Drainage

The indications for drainage of a pseudocyst are symptom- and infection-driven, and not merely the size or presence of a pseudocyst by imaging studies. Asymptomatic patients even with collections of ≥6 cm are observed with little risk of complications such as rupture, infection, or bleeding.[4]

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Progressive enlargement of a collection is one exception to symptoms that is cited as an indication for drainage.[1]

Pre-drainage Evaluation

Before undertaking drainage of a pseudocyst, a predrainage evaluation is performed to:

1. Establish whether a "masquerader" such as a cystic neoplasm or other entity is present.[5] The distinction between a cystic neoplasm is based upon clinical presentation, as there is usually an absence of a well-defined antecedent clinical pancreatitis in patients with cystic neoplasms. Imaging studies such as CT, magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) are also helpful in allowing this distinction to be made. Rarely, it may not be possible to distinguish the two.
2. Establish that the collection does not contain significant solid debris.
3. Establish the relationship of the collection to surrounding lumenal and vascular structures.
4. Consider underlying etiologies such as pancreatic cancer, autoimmune pancreatitis,[6] and intraductal pancreatic mucinous neoplasms.

A contrast-enhanced abdominal CT allows assessment of the precise location of the pseudocyst in relation to the stomach and duodenum and potential intervening vascular structures for transmural drainage. Additional studies may include:

1. Endoscopic ultrasonography (EUS).
2. MRI with or without MR cholangiopancreatography (MRCP) for the detection of solid debris,[7] so that plans for removal and/or alternative drainage strategies can be chosen.

Drainage Techniques

Pseudocysts may be drained transpapillarily, transmurally, or using a combination of the two. The decision of one approach over the other depends on the size of the collection, proximity to the stomach or duodenum, and ability to enter the pancreatic duct and/or reach the area of disruption. The decision to use combined transmural and transpapillary approach for large collections is individualized. The combined approach has not been shown to be superior to transmural drainage alone. Most pancreatic ductal side branch leaks will resolve during transmural drainage. However, in patients with major main ductal leaks it is possible that stent placement may allow one to maintain ductal integrity after transmural drainage, although this is unproven.

Transpapillary Drainage

When the pseudocyst communicates with the main pancreatic duct a pancreatic endoprosthesis can be placed with or without pancreatic sphincterotomy. This approach is useful for drainage of pseudocysts measuring ≤6 cm that are not approachable transmurally.[1] The stent is placed across the leak and obstructive processes such as stricture or stones.[8] The stent diameter is usually 7 Fr. Endoscopic therapy of underlying strictures and stones may reduce pseudocyst recurrence rate once the stent is removed.[1] The transpapillary approach avoids bleeding and perforation that may occur with transmural drainage, but may induce scarring of the main pancreatic duct.

Transmural Drainage

The type of devices used to puncture through the gastric or duodenal wall into the collection can be divided into cautery and non-cautery devices. There is no standardized transmural drainage approach. Some endoscopists feel that EUS evaluation is mandatory for drainage of pseudocysts,[9] although the superiority of EUS-guided versus non EUS-guided drainage has not been demonstrated.[10] Approximately 50% of all respondents to a recent survey of transmural drainage practices claimed to use EUS-guided transmural drainage.[11] EUS imaging may theoretically reduce complications related to transmural entry by avoiding bleeding and perforation.[10,12] EUS can be used to localize the collection in relationship to surrounding structures and endoscopic landmarks or for puncture under real-time guidance similar to EUS-guided fine-needle aspiration (FNA).[9,13,14] The lack of EUS availability, however, does not preclude transmural drainage except in the instances such as a small "window" of entry based on CT, especially in the absence of an endoscopically defined area of extrinsic compression, or in unusual locations,[1] coagulopathy or thrombocytopenia, documented intervening varices,[15] and failed transmural entry using non EUS-guided techniques.

The collection is entered at a point of endoscopically visible extrinsic compression using electrocautery or needle.[16–18] Once entry is confirmed, the transmural tract is balloon dilated to 8–10 mm to allow placement of one or two 10-Fr stents. The tract is not enlarged using cautery and

a sphincterotome because of an increased risk of bleeding. Double pigtail stents are placed because they are less prone to migrate into or out of the collection, and straight stents are associated with delayed bleeding complications.[19] I routinely place one to two short length (3–5 cm) 10-Fr double pigtail stents during transmural drainage.

Results of Endoscopic Therapy of Pancreatic Pseudocysts

There are no prospective studies comparing endoscopic drainage to conservative (medical) therapy, percutaneous drainage, or surgical drainage. The success rates, recurrence rates, and complication rates after endoscopic drainage of pseudocysts are variable, likely because the patient populations and interventions in most series are heterogeneous. Some patients will require several endoscopic procedures. The decision to continue endoscopic therapy is individualized based on underlying medical problems, patient preference, and whether additional endoscopic therapies to remediate the lack of improvement are feasible. Nonetheless, successful drainage is achieved in approximately 75–100% with complication rates of about 5–10% and recurrence rates of 5–20%.[1,15,20] An advantage over percutaneous drainage is the avoidance of external fistula. Operator experience may play a role in the outcome after endoscopic therapy of pseudocysts.[21]

In my experience of draining over 200 pseudocysts at two institutions, successful drainage is achieved in well over 90% of cases.[18,22] The overwhelmingly predominant method of drainage has been transmural, but with an emphasis on identifying and treating pancreatic ductal abnormalities. The complication and recurrence rates have decreased to less than 10%.

Management of Recurrences

The precise role of additional endoscopic therapy for management of cyst recurrences is unknown and is based on patient preference and operative status. Additional endoscopic procedures can be undertaken, especially if there are remediable ductal abnormalities. I have undertaken transduodenal drainage with good long-term response for patients with disconnected pancreatic ducts whose collections have recurred following transgastric drainage. However, in patients with disconnected pancreatic ducts and pseudocysts at the tail in whom only transgastric drainage is possible, surgical therapy may be a better long-term approach, as the gastric wall does not stay open after stent removal. In non-operative candidates transmural stents may be left in place indefinitely to prevent recurrence.

Complications of Endoscopic Therapy of Pancreatic Fluid Collections

Life-threatening complications may arise after attempted endoscopic drainage of pseudocysts, which may require surgical and interventional radiological support. Bleeding after transmural drainage may be managed supportively, endoscopically, surgically, or with angiographic embolization. Infectious complications usually occur from inadequate drainage of fluid and/or solid debris, and are frequently manageable by additional procedures. Endoscopic therapy may be associated with complications and/or failures that require surgical management. It is possible that the outcome of surgical therapy may be adversely altered when compared to those patients undergoing primary surgical therapy.[23]

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Impact of Changing Epidemiology of Gastroesophageal Reflux Disease on its Diagnosis and Treatment

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Abstract Gastroesophageal reflux disease (GERD) has emerged as one of the most common diseases in modern civilization. This article reviews selected changes in epidemiology of GERD during the past decade and provides information on treatment options with a focus on the impact of GERD and potential role of laparoscopic antireflux surgery in patients with diabetes mellitus, obesity, liver cirrhosis, at the extremes of life age and in immunocompromised individuals such as liver and lung transplant recipients.

Keywords Gastroesophageal reflux disease · Diabetes mellitus · Immunocompromised individuals

Introduction

GERD is one of the most common diseases in modern civilization.[1,2] It is closely linked to changes in life style.[3] Many factors contribute to this increasing prevalence of GERD including eating habits and modern processing and preparation of food and drinks.[4] The role of *Helicobacter pylori* (HP) continues to be evaluated, and to date, its role in the pathogenesis and therapeutic effects in GERD remain controversial.[5,6] Obesity and diabetes mellitus (DM) have been recognized as risk factors for GERD.[7,8] If untreated, GERD can progress to severe complications including esophagitis, esophageal strictures, and probably Barrett metaplasia and pulmonary and laryngeal disease.[9] Medical therapy with proton pump inhibitors (PPI) provides effective healing in more than 85% of patients with erosive disease.[10] The development of minimally invasive laparoscopic surgery for the treatment of GERD has evolved into an effective and more acceptable treatment option for GERD than open surgical approaches. We now have over a decade of available experience with this technique which has an established therapeutic efficacy with durable effects.[11]

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Epidemiology of Gastroesophageal Reflux Disease

Whereas the incidence of gastric ulcer and duodenal ulcer and gastritis has constantly declined during the past decades GERD has become more prevalent.[12] Dent et al. recently summarized 15 studies on the epidemiology of GERD demonstrating that there remains a lack of consensus in the definition of GERD and that GERD is a highly prevalent disorder with 10–20% of individuals affected in western civilization.[1] Genetic, demographic, and behavioral factors impact the incidence and course of GERD. Comorbid factors have been identified, but it remains to be discussed if they are underlying conditions or consequences of GERD or both.[1] Gastrointestinal, pulmonary, laryngeal, metabolic, neurological, and psychiatric conditions have been linked to GERD.[2] GERD appears to be significantly more common in western countries. When defining GERD as twice weekly reflux over several months, 10–20% of individuals in Western civilization are affected, which is significantly

higher than in the Asian population with 5%. These epidemiological differences seem to reflect different life styles, eating habits, and prevalence of HP.[13] Fass et al., in large prospective Americaparticularlyparticularlyn cohort study, reported that 25% of investigated individuals experi enced nocturnal reflux symptoms.[14] In this study, GERD was strongly associated with an increased body mass index (BMI), carbonated soft drink consumption, snoring and daytime sleepiness, insomnia, hypertension, asthma, and usage of benzodiazepines.

Ulcer disease and gastritis are associated with HP infection. Better hygiene and chlorination of drinking water have led to a declining prevalence of this bacterium in civilized countries.[15] Interest in eradication of HP lies on the fact that this bacterium is considered as a class I carcinogen.[16] Although some studies, including a recent one from Sweden, have found HP-positive individuals to be at higher risk for symptomatic GERD and erosive esophagitis[12]; overall, the available epidemiological data indicate a negative correlation between *H. pylori* and GERD. This association is particularly more established for the CagA-positive (more virulent) strains of HP.[17] Thus, it remains speculative whether this negative association affords a protective effect against GERD, as HP lowers gastric acid production. There is also conflicting data on the effects of eradication of HP on GERD. Thus, the exact role of HP in GERD is still a matter of debate and no final recommendations have been established whether to eradicate HP associated with GERD.

Obesity and a hiatal hernia predispose to GERD.[12] Other conditions that have been linked to GERD include dietary indiscretion, coffee, smoking, and alcohol use.[14,18,19] Some antidepressants and nonsteroidal anti-inflammatory agents are known to interfere with gastric acid secretion and gastric mucus production and motility.[20,21] However, their role in GERD, if any, still requires critical evaluation.

Pathophysiology of GERD

GERD originates from a disturbance in the structure and function of the lower esophageal sphincter (LES) barrier.[22] Anatomical or structural abnormalities occur often in the presence of a hiatal hernia and physiological predispositions derive from motility disorders of the LES and esophageal body.[23] Dysfunctional esophageal motility coupled with a weak LES can cause uncoordinated propulsion of food, regurgitation of food and acid into the esophagus, particularly after meals, and in the horizontal position, an inadequate acid/bile clearance from the esophagus.[24] Esophageal motility and gravity facilitate esophageal clearance and adequate gastric emptying represents a further physiological means to decrease GER.[25] Saliva, which is rich in bicarbonate, coats the esophageal epithelium and the production of mucus, prostaglandins, and epithelial growth factors help to prevent damage to the esophageal mucosa. Anatomically, the length of the intra-abdominal esophagus, the phrenoesophageal ligaments, the gastric mucosal "rosette," and the esophageal hiatus (a sling formed by the crura of the diaphragm causing a pinchcock effect), all contribute to a high-pressure zone at the lower esophagus. This high-pressure zone forms the lower esophageal sphincter (LES), a physiological rather than a true anatomical sphincter. Pressures at the gastro-esophageal junction (10–30 mmHg) are greater than gastric luminal pressure (5 mmHg). This prevents retrograde passage of gastric contents. The acute angle of His (made by the esophagus and the axis of the stomach) and the above physiologic factors all contribute to limit the volume and frequency of gastric contents refluxing into the esophagus.[22,23] Thus, GER results from esophageal motility disorders, an anatomical or physiological defect in the diaphragmatic component or from increased intra-abdominal pressure. The recent increase in the incidence of GER can be attributed to all three components given the changing demographics and the changing life style in western civilization.[26–28] Furthermore, alterations known to occur in gastric emptying in diabetes[8] and increase in prescription medications to treat a variety of conditions with calcium blockers, anticholinergic agents, or theophylline may disrupt the functional LES barrier and contribute to GERD. Transient relaxations of the LES are the most common accompaniment of GERD.[29] Thus, it is appealing to speculate that carbonated beverage that may increase belching may also promote GERD.[14]

Pregnancy is a well-known trigger for GERD. The mechanisms involved in GERD in these subjects have been insufficiently understood. Increased intra-abdominal pressure may be one factor, although hormonal theories have also been proposed.[30] The increase in intra-abdominal pressure theory serves as a model for other conditions such as obesity, large intra-abdominal masses, and ascites.[31–33] As GERD is reversible after delivery, weight loss should also improve GERD as should treatment of ascites or removal of large intra-abdominal masses.[34,35] It has been hypothesized that the incidence of GERD in Asia might increase substantially with an increase in the average BMI.

GERD in Obese Patients

The significance of the epidemic of morbid obesity in the USA has recently been addressed.[36] Currently, approximately one-fourth of the US population is affected by obesity. This has increased dramatically during the past

decade and affects more and more young individuals and children. It has been suggested that obesity, to a large extent, is responsible for the higher incidence of GERD in the US. Population estimates indicate that obesity is a more prevalent condition in the USA with 20% affected vs 10% in Europe and 5% in Asia.[1,37] Symptoms improve after weight loss, and successful bariatric surgery has a positive effect on GERD.[38] Therefore, as a general approach, loss of excessive weight continues to be recommended as a first step in the treatment of GERD.[39] If intensive medical therapy, usually involving double-dose PPI and life-style changes are unsuccessful, and the diagnosis of GERD is objectively established (endoscopy, pH-metry, and manometry), carefully selected morbidly obese patients may be offered a bariatric procedure. Gastric banding may function as an antireflux procedure and can achieve good weight loss in many patients. Nevertheless, the esophagus must be mobilized to create adequate intra-abdominal length. Crural repair, together with gastric banding, has been reported to produce good results.[40,41] The limitation of gastric banding in patients with GERD is the presence of a motility disorder of the esophagus. In these cases, gastric bypass may represent a better alternative. Other procedures such as sleeve resection, biliary pancreatic diversion, and vertical banded gastroplasty have been used. For certain patients in whom bariatric surgery is deemed not appropriate, and medical therapy is unsuccessful, fundoplication may be indicated. Surgery in these patients may be difficult. Placement of ports can be challenging, and extra long devices might be required. In obese patients, there may be excessive fat around the stomach and esophagus. The left lateral liver segments can be very large. This might hinder retraction of the liver. Such fatty livers are rigid, and the capsule can easily be injured resulting in hemorrhage. Reports from academic centers indicate similar long-term results after fundoplication in obese and non-obese subjects.[42] Whether physicians in community centers obtain the same outcomes has not yet been evaluated. Patterson et al.[43] reported that GERD improved after fundoplication and after bariatric surgery in obese patients; however, due to the beneficial effects of weight loss after gastric bypass, they favor this procedure over anti-reflux surgery.

GERD in Children

GERD can manifest as early as infancy and is frequently associated with pulmonary symptoms.[44] It is a frequent condition in preterm infants.[45] This is due to the fact that the LES matures only after the 31st week of gestation. Other factors that predispose to GERD in children are neurological disorders, in particular, when the vagus nerve is involved which causes motility disorders of the esophagus and delayed gastric emptying. Syndromes such as Cornelia De Lange syndrome—a dominantly inherited disorder characterized by multisystem involvement, cognitive delay, limb defects, and characteristic facial features due to chromosome rearrangements—are associated with GERD. Other factors include hyperrelaxation of the diaphragm and spasticity of the abdominal wall. Up to 80% of children with esophageal astresia suffer from GERD depending on the type of atresia and the length of the atretic segment.[46] Symptoms at this early age frequently include aspiration and recurrent respiratory infection and failure to thrive due to malnutrition.[45] Twenty-four-hour pH-monitoring, endoscopy, and radiography with gastrografin are used to make a diagnosis. In many cases, GERD at this age is associated with a large hiatal hernia. The first step in therapy is PPIs and the establishment of adequate intake of food. If failure to thrive persists, surgery may be required. Other indications for surgical therapy are bronchopulmonary dysplasia, aspiration pneumonia, sporadic apnea, esophageal strictures, and severe emesis.[45] The Nissen fundoplication is the preferred approach in most published series; however, other techniques have been suggested such as the Toupet, Thal, Lortat-Jacob, and Rosetti procedure.[47,48] Recently, laparoscopy has emerged as a viable surgical option in small children. The reduction in operative time and better exposure of structures has been emphasized, and the learning curve is short.[49] In older children, diagnosis and treatment of GERD does not differ from adults.[50] Liu et al.[51] recently reported on a small series of children undergoing a successful Stretta procedure for GERD.

GERD in the Elderly

In individuals of advanced age, GERD is often associated with a hiatal hernia, in particular, of the paraesophagal type.[52] Other factors contributing to GERD in the elderly are neurological diseases such as stroke and degeneration of the vagal nerves and medications such as anticholinergic agents or calcium-blockers for the treatment of cardiovascular disorders.[53] This study showed that reflux in older patients is complicated by disordered esophageal motility, and it was concluded that this impaired motility may decrease acid clearance, result in more difficult disease control, and may render these patients susceptible to GERD complications. Many epidemiologic studies have excluded individuals older than 75 years, and therefore, little is known of the specific prevalence and incidence of GERD in the elderly. Symptoms differ from younger individuals with a higher prevalence of noncardiac chest pain in the presence of a large hiatal hernia and the other extraesophageal manifestations of GER.[52,54,55] Therefore, cardiac and pulmonary causes of chest pain must be excluded. Significant

motility disorders are common, whereas pH monitoring can be normal due to reduced acid production. In contrast, biliary reflux seems to be more common. Elderly patients benefit from fundoplication, and hernia repair and laparoscopy can be safely carried out with similar mortality and morbidity as in younger patients.[56–58]

GERD and Diabetes Mellitus

The number of diabetics is rising parallel to the epidemic of obesity. Whereas the age-adjusted prevalence of diabetes per 100 adult population within the United States was less than 4% in 1994, this increased to >6% in 2003 for most states. Type I and type II DM both cause severe motility disorders of the gastrointestinal tract.[59–61] This can involve the esophagus and the stomach. A high prevalence (28%) of abnormal gastroesophageal reflux is seen in asymptomatic insulin-dependent diabetic patients as reported by Lluch et al.[60] In this study, the presence of abnormal gastroesophageal reflux in diabetic patients was associated with the existence of cardiovascular autonomic neuropathy. In a Japanese cohort reported by Nishida et al.,[8] the incidence of GERD in type II diabetics was 25%. Obesity, longer duration of diabetes, and peripheral neuropathy were predictors for the development of GERD. Rosztoczy demonstrated that long-standing type I DM results in significant damage to the LES. They found that diabetic patients had decreased peristaltic wave amplitude, prolonged duration, decreased wave propagation velocity, and increased number of simultaneous contractions in the esophageal body, and decreased LES pressures with prolonged relaxation compared to the age- and sex-matched controls.[62] Notably, symptoms in these patients were subtle when compared to the significant abnormalities in pH monitoring and esophageal manometry. If a profound disorder of gastric emptying (diabetic enteropathy) is present, fundoplication may not satisfactorily improve symptoms, despite the fact that fundoplication has been shown to speed gastric emptying.[63] The role of gastric emptying in the development of GER is not clearly established.[64–66] In the case of severe gastroparesis the use of pyloroplasty or a gastric pacemaker has been suggested.[67,68] Recently, Kinekawa et al. reported on the successful usage of aldolase reductase inhibitors (ARIs) in eight type II diabetics suffering from GERD. The study cohort was small; however, ARIs have also been successfully used in other settings of secondary complications of DM. ARIs interfere with polyol pathway hyperactivity, and as far as diabetic neuropathy is concerned, the significance of polyol pathway hyperactivity has been most extensively investigated. A beneficial effect of ARIs on the development of autonomic and somatic diabetic neuropathy has been reported in several clinic trials.[69,70] Erythromycin has been suggested for the treatment of severely delayed gastric emptying; however, beneficial effects are frequently temporary.[71] In type II diabetics who are obese, weight loss should be the first step together with acid blockers and surgery as a second option.[43] Spivac reporting the effects of gastric banding in a large series of obese patients, also noted that there was an 87% reduction of GERD together with a significant reduction on the incidence of DM.[38] DM is not considered a contraindication for antireflux surgery but other complications of DM such as coronary artery disease might be the contraindication for surgery. Perioperative antibiotic prophylaxis should be considered in these patients who are at increased risk for infection. Since diabetic patients have a higher prevalence of steato-hepatitis, a large fatty liver, much like in obese patients, may present challenging technical difficulties for LARS in these patients.

GERD in Immunocompromised Individuals

Immunocompromised patients may be at increased risk to develop GERD. This includes individuals with acquired immunodeficiency syndrome, patients on steroids, solid organ and stem cell recipients or cancer patients.[72–74] Also, patients awaiting organ transplantation might suffer from GERD due to their underlying debilitating condition associated with terminal organ failure.[75,76] Typical GERD symptoms can occur from other causes including immunosuppressive or antitumor therapy, and in particular, infectious complications. Opportunistic infections that involve the esophagus are cytomegalovirus disease, herpes simplex virus and varicella zoster virus infection, and esophageal candidiasis.[72,77,78] Also, necrotizing esophagitis has been reported in immunocompromised patients.[79] Therefore, during endoscopy, these infections must be excluded, and biopsies must be sent for microbiological study. Once the diagnosis of GERD is established, the principles of treatment do not differ from immunocompetent hosts. However, an interdisciplinary approach is needed. Change in the immunosuppressive regimen in some cases might be useful, in particular, withdrawal of steroids. Upper gastrointestinal symptoms must also be expected when using mycophenolic acid and tacrolimus.[80] If patients receive "target of rapamycin inhibitors" such as Sirolimus and Everolimus, which are new immunosuppressive agents with potent antiproliferative capacity, short-term changeover to another immunosuppressive drug should be performed as severe wound healing disturbances can occur.[81] The fundoplication can possibly disintegrate, and closure of the diaphragmatic defect can fail.[82] In immunocompromised individuals, in contrast to the normal host perioperative antibiotic, prophylaxis is of benefit.

GERD and Lung Transplantation

Annually, more than 500 lung transplants are performed worldwide. The first report of a close link between GERD and complications after lung transplantation was published almost 10 years ago, and since then, more and more evidence has been collected that GERD plays an important role in the pathology of terminal lung failure.[83–85] Bendon et al. reported that in pediatric lung recipients, the prevalence of GERD was almost 100%, and those with bronchiolitis obliterans syndrome (BOS) had more severe reflux.[86] However, many of these children were asymptomatic. Bile reflux into the graft seems to have a particularly detrimental effect. The concept that BOS might rather be a manifestation of GERD than chronic rejection has been suggested by Verleden et al.[87] Some centers perform a routine transthoracic fundoplication after implantation of the lung: alternatively, laparoscopic fundoplication after lung tranplantation has been reported to reduce chronic damage to the graft and to improve survival.[88] Prevention of micro- and macroaspiration has been proposed by Hartwig et al.[89] to be the background for this improvement. Fundoplication might be an important step in lung recipients as there is a significant increase in GER after lung tranplantation, as measured objectively by 24-h pH studies, despite a lack of symptoms in most patients.[90] The knowledge of a link between GERD and lung allograft dysfunction and its reversibility has profoundly impacted the understanding of the pathology of some pulmonary diseases such as emphysema and bronchiectasia and will likely expand the indications for laparoscopic antireflux surgery.[91–94]

GERD in Patients with Liver Cirrhosis and Liver Transplant Recipients

Little data are available for these patient populations concerning the prevalence of pre-GERD, optimal therapy, and the effects of LARS. More than two million individuals in the US suffer from liver cirrhosis. In 2004, more than 2000 liver transplants were performed in the US. Zaman et al.[95] focused on the prevalence of upper and lower gastrointestinal tract findings in liver transplant candidates undergoing screening endoscopic evaluation and found that the frequency of esophagitis pretransplant was 13%, and 2% had Barretts esophagus. Karasu et al.[96] found a high incidence of esophagitis increased from a baseline of 7.5 to 22% post-transplant, which the authors partially attributed to antirejection medications. They also emphasized that pretransplant ascites with increased intra-abdominal pressure, sclerotherapy for varices and the surgical trauma with possible injury to the phrenic nerve during dissection and cross clamping of the suprahepatic inferior vena cava should be considered factors responsible for this high incidence of transplant esophagitis. Liver disease is associated with portal hypertension and GERD has been suggested to play a role in acute hemorrhage from esophageal varices.[32] The potential damaging effects of GERD in patients with esophageal varices and the role of GERD in precipitating GI hemorrhage in this population has not been critically evaluated. Similarly, the impact of prophylactic acid inhibition therapy to prevent variceal hemorrhage has not been evaluated. On the other hand, no major negative effects seem to occur on esophageal functional parameters after the endoscopic treatment of esophageal varices.[97,98] For patients with esophageal varices dissection of the esophagogastric junction might be contraindicated. On the other hand for patients with Child A cirrhosis and treated varices, antireflux surgery can be safely carried out by an experienced laparoscopic surgeon.[99,100] Diagnosis in patients with esophageal varices is difficult as pH-metry and manometry may induce variceal bleeding.

Barrett Esophagus, Esophageal Cancer and Fundoplication

Several studies have implied that long-term reflux disease causes changes in the epithelium of the distal esophagus including metaplasia, Barrett esophagus, dysplasia, and possibly esophageal cancer.[101–103] These changes gradually evolve, and it takes decades until low-grade dysplasia transforms into high-grade dysplasia. The relative risk of adenocarcinoma in the setting of Barrett's esophagus is relatively low at 0.4%/year.[104] However, recent studies have noted an increase in the incidence of distal esophageal adenocarcinoma that has been attributed to GERD.[103,104] If acid or bile reflux are responsible for these changes remains a matter of debate. It also is unclear if medical acid suppression can prevent these changes from occurring.[105] Therefore, it is tempting to consider that an antireflux procedure by completely preventing reflux might be able to impact the development of these changes in the distal esophagus.[106] Small surgical series have reported some potentially favorable effects.[99,100] Rossi et al. recently demonstrated a potential benefit for patients who underwent surgery as opposed to medical treatment in terms of progression of dysplasia.[107] Thus far, neither medical nor surgical therapy has been shown to reduce or prevent the incidence of high-grade dysplasia or esophageal cancer.[108] It is not clear why there are differences in outcome from the studies cited. Some possible explanations may include variable study design. Furthermore, these malignant changes are uncommon, and it would require huge patient

numbers to reach statistically significant differences. Moreover, no prospectively randomized studies are available, a variety of antireflux procedures and expertise have to be considered, and in many studies, the competency of the wrap was not assessed. Finally, patient compliance with use of medications was not tested, and other confounders such as smoking and alcohol use were not included in the analysis. Finally, when looking at the incidence of cancer after fundoplication, it may not be clear from series whether some patients may have had undetected early cancer or dysplasia at the time of surgery. At present, no final conclusion can be made on this issue, and it cannot be recommended to perform preemptive fundoplication to prevent esophageal carcinoma.[109–111] Recently, endoscopic ablation of Barrett mucosa after laparoscopic fundoplication has been suggested as an alternative approach.[112] Duodenal diversion, as suggested by Braghetto et al.,[113] appears to be a radical approach for this problem.

Conclusion

GERD represents one of the fastest growing diseases affecting the alimentary tract.[1] Reflux of gastric content into the esophagus not only causes injurious damage to the esophageal mucosa but also seems to be associated with a plentitude of secondary effects including diseases of the teeth, the upper respiratory tract, and the lungs.[93,114–116] Thus, GERD is now being treated and recognized with increased frequency not only by gastroenterologists and surgeons but also to pulmonologists, pediatricians, and dentists. The epidemic of obesity and diabetes mellitus in modern civilization has dramatically increased the number of patients suffering from GERD. Although weight loss remains a cornerstone for the treatment of these individuals, there is insufficient information available, or appropriate guidelines for the optimal management of GERD in this patient population.[117] The exact role of HP and GERD is still a matter of debate. The available epidemiological data indicate a negative correlation between *H. pylori* and GERD. There is also conflicting data on the effects of HP eradication of GERD. There remain more questions than answers.[118] The same is true for the interplay between HP, Barrett esophagus, epithelial dysplasia, and adenocarcinoma of the esophagus in conjunction with GERD.[119,120] The debate if properly treated GERD can prevent these changes and the development of malignancies of the esophagus is ongoing, and even meta-analysis of surgical therapies has yielded equivocal results. New endoscopic techniques for the treatment of GERD have emerged.[121] Currently, both medical therapy and surgical treatment provide effective and long-term beneficial effects for the treatment of GERD.[122–124] Endoscopic therapies have recently emerged as promising therapies for the treatment of GERD.[122,125] However, before they can be adopted in the daily practice of medicine, critical studies involving sham trials and long-term durability effects and careful evaluation of side effects need to be completed. Laparoscopic fundoplication is successful in most cases if appropriate principles of operative therapy are followed. Laparoscopic antireflux surgery can be safely performed in patients of operative therapy if followed. Laparoscopic antireflux surgery can be safely performed in patients with complex medical conditions and in the elderly and very young children.

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Pancreatic VIPomas: Subject Review and One Institutional Experience

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Abstract VIPomas are rare pancreatic endocrine tumors associated with a well-defined clinical syndrome characterized by watery diarrhea, hypokalemia, and metabolic acidosis. The objective of this study was to review a single institution's experience with VIPomas, as well as to review the English literature. A retrospective review of the Johns Hopkins pancreatic database revealed four cases of VIPoma, with three patients being male. All patients presented with watery diarrhea, hypokalemia, hypercalcemia, and acidosis. All patients had no family history of multiple endocrine neoplasia. Computed tomography revealed the primary pancreatic tumor in all patients, with three tumors located in the tail of the pancreas. One tumor involved the entire pancreas. Computed tomography and/or octreotide radionuclide scans identified hepatic metastasis in three patients. Mean serum vasoactive intestinal polypeptide levels were 683 pg/ml (range 293 to 1,500 pg/ml). All patients underwent resection of the pancreatic primary tumor. Two patients also had simultaneous liver resections. All patients had evidence of malignancy as defined by the presence of metastatic lymph nodes and/or hepatic metastases. Two patients had complete resolution of symptoms after surgical resection. One patient required radioablation of liver metastases and adjuvant octreotide therapy for control of symptoms. One patient died of progressive metastatic disease 96 months after surgery, whereas the other three remain alive. Extended, meaningful survival can be achieved for VIPoma patients, combining an aggressive surgical approach with additional strategies for treatment of unresected disease.

Keywords VIPomas · Diarrhea · Primary pancreatic tumor

Introduction

Vasoactive intestinal polypeptide (VIP)-secreting tumors of the pancreas are rare islet cell tumors associated with secretory diarrhea. The annual incidence of these tumors is estimated to be about 1 per 10,000,000 individuals in the general population.[1] At the time of presentation, over 70% of patients have metastases identified,[2] and the great majority of these tumors are malignant based on the presence of either hepatic, distant, or lymph node metastases.[3] Ninety percent of VIPomas in adults are primary tumors of the pancreas, although they have been described in the colon, bronchus, adrenals, liver, and sympathetic ganglia.[4] In children, however, these tumors are most commonly found in the adrenal glands and sympathetic ganglia. The clinical syndrome that accompanies this tumor most commonly includes watery diarrhea, hypokalemia, and achloryhdria (or metabolic acidosis); thus, it is commonly referred to as the WDHA syndrome. Other names for the syndrome include watery diarrhea syndrome, pancreatic cholera syndrome, endocrine cholera, and the Verner–Morrison syndrome.

The first description of watery diarrhea and hypokalemia in relation to a pancreatic islet cell tumor was by Priest and Alexander in 1957.[5] They described a 56-year-old woman that had previously undergone resection of an islet-cell tumor from the body and tail of her pancreas. At the time of resection her only symptom was left-sided abdominal pain.

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Six years later, she presented with symptoms of intractable watery diarrhea and hypokalemia. She was medically managed for approximately 1 year before her death. At autopsy, she was found to have a recurrent islet-cell tumor in the pancreatic remnant with no evidence of metastases. In 1958, Verner and Morrison described two male patients, a 67-year-old and a 19-year-old, who had similar presentations with refractory watery diarrhea and hypokalemia. Both patients died secondary to cardiac arrhythmias related to their hypokalemia and each patient had a pancreatic islet cell tumor without metastases at the time of autopsy.[6] In 1973, Bloom et al. found an association between this syndrome, an elevated plasma VIP level, and an increased tumor content of VIP.[7] In 1983, Kane et al.[8] successfully reproduced the clinical syndrome by infusing five healthy human subjects with porcine VIP to achieve VIP levels similar to those of patients with VIPomas. They found that all the subjects developed profuse watery diarrhea within 4 h of infusion, thus solidifying the assertion that VIP is the mediator of the WDHA syndrome.

Vasoactive intestinal polypeptide is a 28-amino acid polypeptide with close structural homology to secretin. Unlike the hormone secretin, VIP normally functions exclusively as a neurotransmitter. In addition to being present in enteric neurons, VIP is also present in neurons of the brain, spinal cord, lung, urogenital system, and other endocrine organs. Vasoactive intestinal polypeptide has a half-life of less than 1 min in the circulation. Plasma levels in normal individuals are quite low and unresponsive to the ingestion of a meal. Among the potential normal actions of VIP are stimulation of enteric smooth muscle,[9] stimulation of pancreatic exocrine and intestinal secretion,[10] inhibition of gastric acid secretion,[11] and modification of immune function and gastrointestinal blood flow.[12] Direct effects on enteric smooth muscle cells and modulatory effects on interneurons have been demonstrated.[13] Two VIP receptors have been cloned: VIP1 (or VPAC1) and VIP2 (or VPAC2) receptors. Both are typical members of the secretin family of G protein-coupled receptors. Vasoactive intestinal polypeptide is also well recognized by the PACAP (or PAC1) receptor. Secretin is recognized weakly by the VIP1 receptor and not at all by the VIP2 receptor.[14] The specific tissue and cellular distribution of these receptors is currently being characterized.

We present our institutional experience with surgically resected pancreatic VIPomas, along with a review of the English language literature describing reports of both surgically resectable and unresectable tumors.

Patients: Clinical History And Management

Patient #1 A 74-year-old male presented to an outside hospital with several months of profuse watery diarrhea. The patient had multiple admissions to the outside hospital for dizziness and dehydration related to his diarrhea. He was repeatedly treated with oral rehydration solutions and electrolyte repletion without resolution of his symptoms. Prior workup had included extensive serologies, esophagogastroduodenoscopy, colonoscopy, fecal leukocytes, clostridium difficile toxin, ova and parasites, quantitative 72-h fecal fat collection, and small bowel series, all of which were negative. Magnetic resonance imaging (MRI) of the abdomen eventually revealed an 11×7×7-cm mass in the tail of the pancreas that abutted the splenic vasculature, stomach, and left adrenal gland, but without clear evidence of local invasion. Octreotide therapy was initiated with good control of his diarrhea and the patient was referred to Johns Hopkins for definitive surgical management.

Abdominal computed tomography (CT) with intravenous contrast was performed to assess surgical resectability of the mass (Fig. 1). The mass compressed and obstructed the splenic vein and displaced the splenic artery. The portal vein, superior mesenteric artery, and celiac artery were patent. His electrolytes, most notably potassium, chloride, and calcium, were all within normal limits. Hormone levels were obtained, which revealed a serum VIP level of 293 pg/ml (normal range 0–50 pg/ml), pancreatic polypeptide (PP) level of 2,087 pg/ml (normal range 51–326 pg/ml), and chromogranin A level of 78 pg/ml (normal range 6–39 pg/ml). His other hormone levels included a normal glucagon, gastrin, and insulin. In addition, the tumor markers CEA and CA19-9 were normal.

The patient underwent a distal pancreatectomy with en bloc splenectomy. The final pathology from this procedure revealed a 14.5-cm well-differentiated pancreatic islet cell tumor, which extended into the peripancreatic soft tissues with involvement of one of eight regional lymph nodes. Immunohistochemical stains of the tumor revealed focally positive staining for VIP (Fig. 2). The patient recovered well, and his serum VIP levels immediately postoperatively and at 1-month follow-up were 40 and 34 pg/ml, respectively. Likewise, his PP and chromogranin levels at 1 month postoperatively normalized to 400 and 31 pg/ml, respectively. The patient is alive, asymptomatic, and disease-free 17 months after his surgical resection.

Patient #2 This 50-year-old woman presented with a 2-month history of diarrhea, vomiting, and anorexia. She was taken to the cardiac care unit emergently following a 10-s episode of asystole. Subsequent evaluation revealed a potassium level of 1.6 mEq/l, a calcium level of 11.7 mg/dl, and a metabolic acidosis (pH 7.25). The patient's watery diarrhea and hypokalemia were believed to be related to a gastrointestinal, endocrine, or renal abnormality, given the broad constellation of signs and symptoms. Thyroid function tests (thyroid-stimulating hormone, T_4, T_3), parathyroid

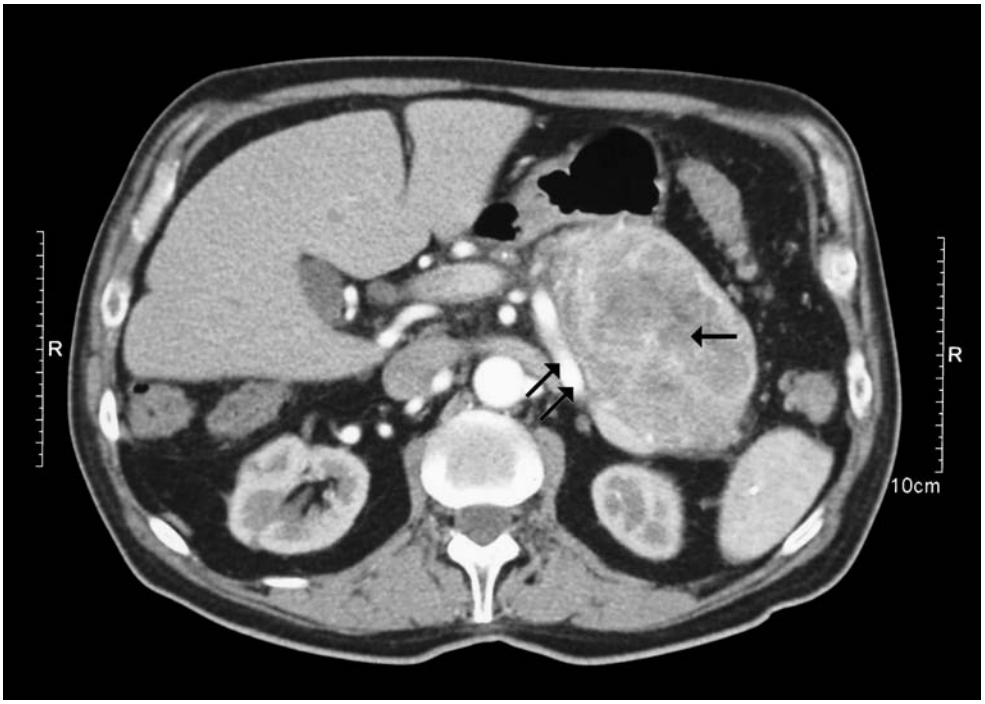

Figure 1 Abdominal CT scan of patient 1 showing large mass of the tail of the pancreas (*arrow*) with displacement of the splenic artery (*double arrow*).

hormone, and serum cortisol were normal. An abdominal CT scan revealed a 3.5-cm mass in the tail of her pancreas and multiple hypodense lesions in the liver, consistent with metastases. Her serum VIP level was 770 pg/ml, with a serum gastrin level of 500 pg/ml. After intravenous hydration and electrolyte repletion, the patient was started on parenteral octreotide in preparation for surgery.

The patient underwent a distal pancreatectomy with en bloc splenectomy, open cholecystectomy, and wedge resection of several hepatic metastases. The final pathology revealed a 4.5-cm islet cell tumor of the body of the pancreas with infiltration into the peripancreatic soft tissues and involvement of one of 14 resected regional lymph nodes. The liver masses measured from 0.5 to 2 cm and were biopsy-confirmed to represent metastatic islet cell tumor. Postoperatively, her serum VIP and gastrin levels declined to less than 35 and 118 pg/ml, respectively. The patient received octreotide therapy for management of her metastatic disease and died 8 years after her pancreatectomy from tumor cachexia related to advanced metastatic disease.

Patient #3 A 66-year-old male presented with a 6-month history of watery diarrhea and a 40-lb weight loss. His laboratory values at the time of presentation were notable for a metabolic acidosis (pH 7.21) and hypokalemia (2.8 mEq/l). His serum VIP level was 169 pg/ml. A CT scan of the abdomen demonstrated an exophytic mass involving the tail of the pancreas measuring 3×5×6 cm without evidence of adenopathy or hepatic involvement (Fig. 3). He also underwent an octreotide radionuclide study, which demonstrated scattered radiotracer uptake in the liver, most consistent with hepatic metastases (Fig. 4).

The patient underwent a distal pancreatectomy with en bloc splenectomy, open cholecystectomy, and resection of segments II and III of his liver. Final pathology of the resected tissue demonstrated a 5-cm malignant endocrine

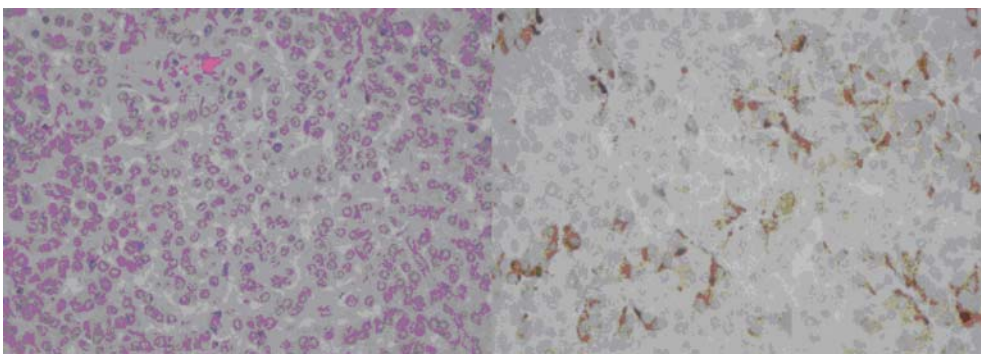

Figure 2 *Left*: Pancreatic VIPoma in patient #1 demonstrating classic features of a neuroendocrine lesion with trabecular architecture and low grade, uniformly round nuclei with finely speckled chromatin (hematoxylin and eosin, ×400). *Right*: Immunohistochemical staining of the tumor demonstrating focal positivity for VIP (VIP immuno stain, ×400).

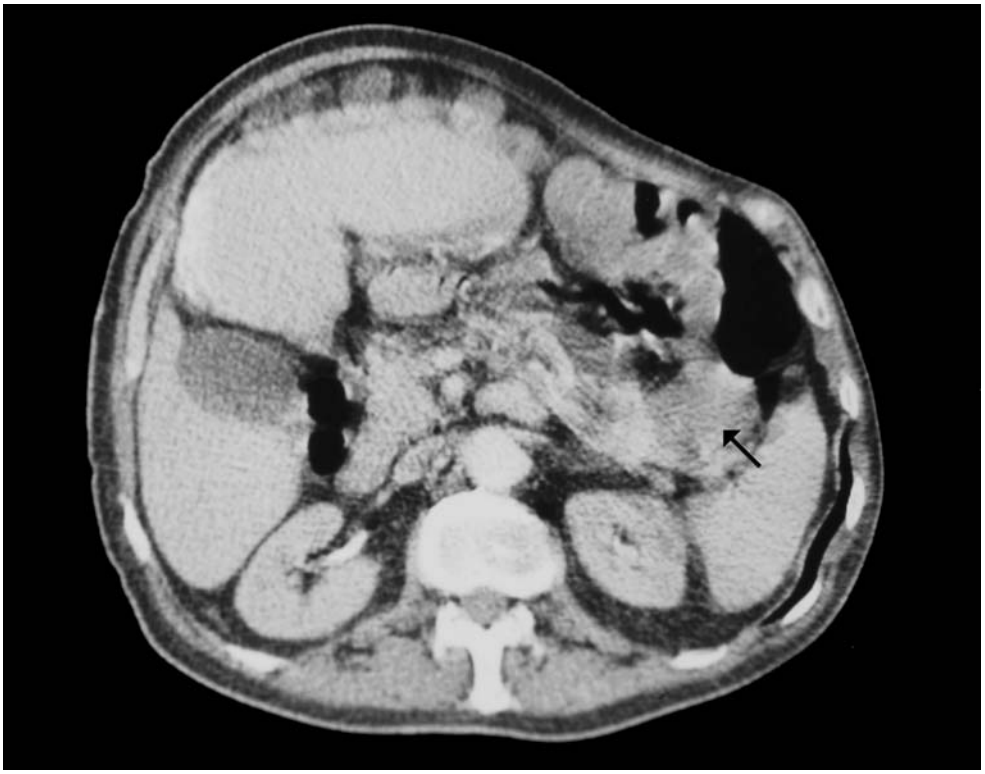

Figure 3 Abdominal CT scan of patient 3 demonstrating a hypodense pancreatic tail mass (*arrow*).

neoplasm of the pancreas with large vessel vascular invasion, invasion of peripancreatic soft tissues, and lymph node involvement. The resected segments of the liver also revealed two foci, measuring 1.7 and 0.3 cm, of metastatic neuroendocrine neoplasm. Immunohistochemical staining was positive for chromogranin, synaptophysin, and neuron-specific enolase, whereas stains for somatostatin, insulin, serotonin, glucagon, and gastrin were negative. An immunohistochemical stain for VIP was unavailable at the time of tissue processing. His postoperative serum VIP level declined to 58 pg/ml and his 1-month follow up VIP level was 32 pg/ml. The patient is still living 68 months after resection of the primary tumor, and had rising VIP levels and recurrent diarrhea. He has since undergone a partial hepatectomy and radiofrequency ablation of persistent metastases with some decline in VIP levels. He is currently receiving long-acting (depot) octreotide treatment, with excellent control of his diarrhea.

Patient #4 A 68-year-old gentleman presented to an outside hospital with increased weakness, weight loss, and an 8- to 9-year history of diarrhea requiring multiple hospitalizations for dehydration. His laboratory values at the time of presentation were significant for an elevated calcium level at 10.7 mg/dl and hypokalemia (3.1 mEq/l). After an abdominal CT scan was suggestive of a pancreatic malignancy, a serum VIP level returned at 1,500 pg/ml. The CT scan showed a large heterogeneous tumor involving the entire pancreas measuring approximately 8 cm in the anteroposterior dimension and 14 cm in width, with multiple hepatic and lymph node metastases (Fig. 5). There was evidence of encasement of the splenic and hepatic arteries by the tumor, with external compression of the portal/splenic vein confluence. The patient was started on octreotide with relatively good control of his diarrhea and was then referred for definitive surgical management.

The patient underwent a pylorus preserving total pancreaticoduodenectomy with en bloc splenectomy. Final pathology demonstrated a malignant neuroendocrine neoplasm measuring 14 cm in maximal dimension, centered in the head of the pancreas and extensively infiltrating the remainder of the pancreas. The lesion extended into the peripancreatic fat, but all resection margins were negative. Sixteen of 29 sampled lymph nodes were positive for metastatic disease. The patient is alive and remains asymptomatic 22 months postoperatively, with stable hepatic metastases.

Literature Review

In our review of the last 25 years of the English language literature, we found 35 individual case reports of patients with pancreatic VIPomas and four case series/reviews. This is the first paper to examine the English language literature so extensively.

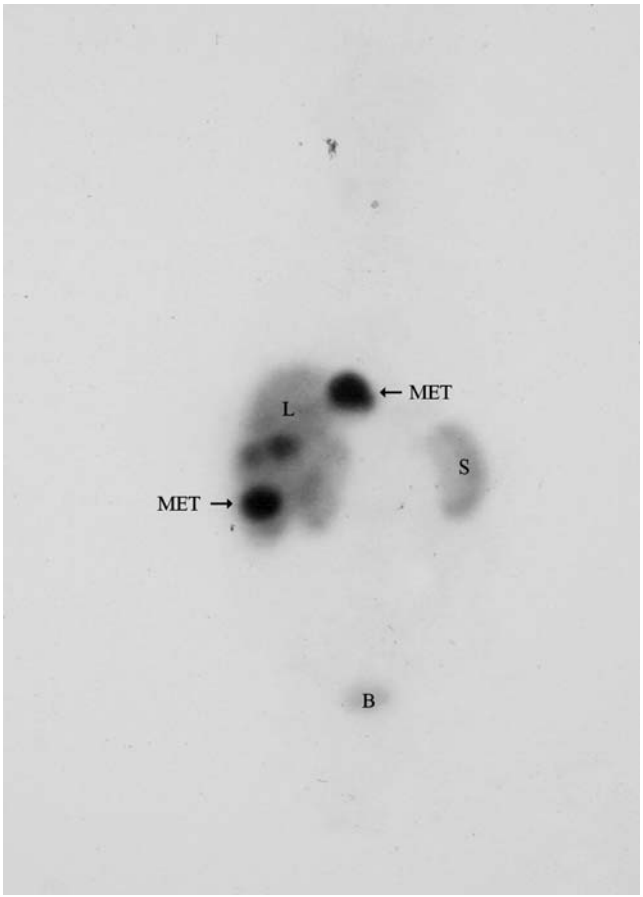

Figure 4 Octreotide radionuclide scan of patient 3. The liver (*L*), spleen (*S*), and bladder (*B*) are seen. Scattered hepatic metastases are evident (*MET*).

Individual Case Reports

The 35 case reports are summarized in Table 1.

Age and sex Thirty five patients were identified with 20 females and 15 males, ranging in age from 11 to 75 years old (mean 48, median 51).

Presenting signs and symptoms The most common clinical and laboratory findings in the 35 patients are outlined in Table 1. As expected, nearly 100% of patients presented with watery diarrhea. Only one patient, presented by Koberstein et al.,[15] did not present with watery diarrhea. This 57-year-old male presented with a paralytic ileus of unknown origin. The patient had a transient episode of loose, melanotic stools several days prior to admission following an episode of prolonged epistaxis. The patient had not mentioned this episode during the initial interview. This unusual presentation, in conjunction with the laboratory findings of hypokalemia, hypercalcemia, and acidosis, which were refractory to intravenous repletion, led the physicians to consider a neuroendocrine etiology such as VIPoma. Indeed, the patient was found to have a mass in the tail of the pancreas, confirmed to be a VIPoma, with serum VIP levels ranging from 173 to 266 pg/ml.

VIP radioimmunoassay Values were reported in 29 of the 35 cases reviewed. The values ranged from 100 to 7,200 pg/ml (mean 1,209 pg/ml, median 632 pg/ml).

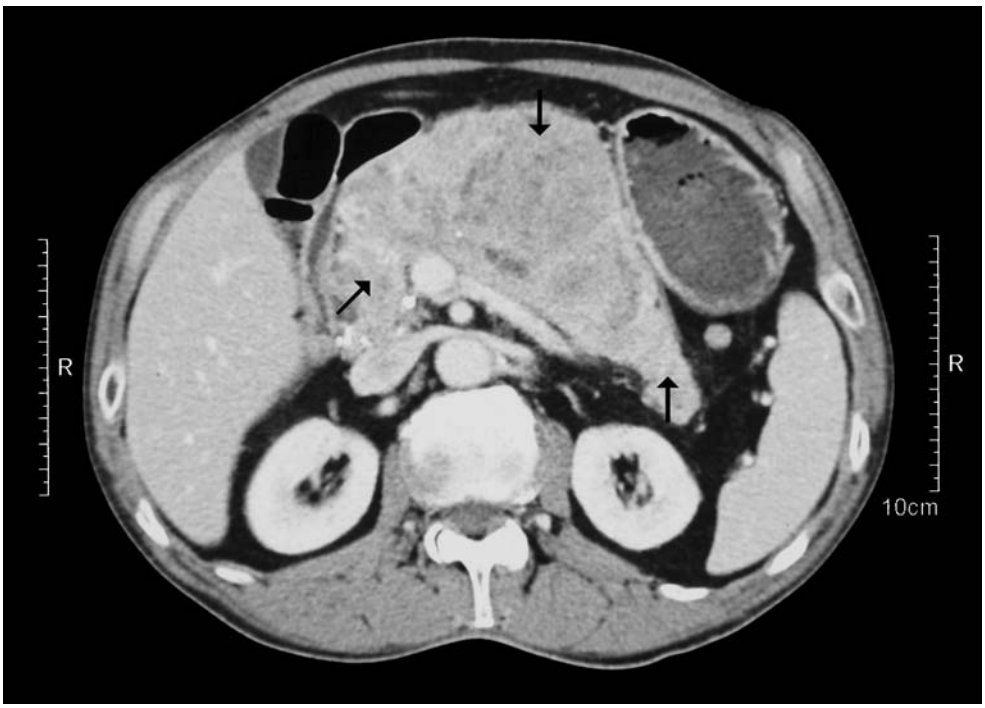

Figure 5 Abdominal CT scan of patient 4. The pancreatic parenchyma is largely replaced by tumor (*arrows*).

Table 1 Individual Case Reports in the Literature and our Four Institutional Cases

References	Year	Age	Gender	Size (cm)	Site	Metatases	Surgery	Symptoms	Imaging	VIP (pg/ml)	Outcome	TSD (Months)
Rood et al.[21]	1988	35	F		Head	Yes	PDD,HG,LR	wd,hk,a	CT	2,400	DOD	48
Cavallo-Perin et al.[34]	1988	55	M		Tail	Yes	None	wd,hk,f	CT	755		
Koberstein et al.[15]	1989	57	M		Tail	No	DP	hk,a,hc,paralytic ileus	CT	266	AWD	
Christensen et al.[35]	1989	60	F		Body		None	wd,hk,a,wtls	CT	632	AWD	12
Tjon et al.[36]	1989	44	F	7	Head	Yes	PDD	wd,hk,ahc,d	CT	412	AWD	6
Venkatesh et al.[37]	1989	54	M		Tail	Yes	DP	wd,hk,a,hc,wtls,d		255	NED	120
Maltese et al.[38]	1990	56	F	10	Head	Yes	PDD	wd,hk,a,wtls,d,hch	Arterio	118	DOD	36
Bramley et al.[39]	1990	41	F		Tail	Yes	DP	wd,hk,f,wtls		1,330	NED	12
Yanagi et al.[40]	1991	20	F	3	Head	No	PDD,S	wd,hk,a,hc	CT	130	NED	2
Brunani et al.[41]	1991	53	F	5	Tail	Yes	DP	wd,hk,wtls		520		
Bani Sacchi et al.[42]	1992	41	M	6	Tail	Yes	DP,S	wdhk,a,ac		1,480		
Bani Sacchi et al.[42]	1992	55	F	8	Tail	Yes	DP,S	wd,hk,a,ac		881		
Bani Sacchi et al.[42]	1992	61	F	9	Head	Yes	PDD,S	wd,hk,a,ac		1,448		
Udelsman et al.[43]	1993	50	M	3	Head	Yes	PDD,HG	wd				DOD
Antonelli et al.[44]	1993	72	F		Tail	Yes	PDD	wd,hk,bp,wtls		100		
Brunt et al.[45]	1994	26	M	5	Head	No	PDD	wd,hk	CT	697		
Cesani et al.[46]	1994	67	F	6	Tail	No	DP,S	wd,hk,hc,d	CT	540		
Crowly et al.[47]	1996	68	F	3	Tail	No	DP,S	wd,hk	MRI	2,667		
Kirkpatrick et al.[48]	1996	63	M	5	Head	No	PDD	wd,hk,hc	CT	228	NED	12
Sofka et al.[49]	1997	32	M	2	Tail	Yes	DP,S,LR	wd,wtls	MRI	365		
Virgolini et al.[50]	1998	38	M	3.5	Tail	No	DP,S	wd,hk,f,d	CT	529	NED	24
Hengst et al.[51]	1998	54	M		Tail	Yes	DP,S	wd,hk,a,hc,hch	CT	452	NED	108
Huang et al.[52]	1998	51	M	4	Head	Yes	Enuc,DP,S	wd,hk,a,f,d,hch	CT		DOD	52
Sjoqvist et al.[53]	1998	30	F		Tail	No	DP,S	wd,hk,a,wtls			NED	36
Nguyen et al.[54]	1999	53	M		Body	Yes	None	wd,hk	CT	3,159	AWD	12
Nguyen et al.[54]	1999	45	M	3	Tail	Yes	None	wd	CT	2,128	DOD	12
Samal et al.[55]	2000	11	F	5	Body	No	DP,S	wd,hk,a,wtls,d	CT		NED	18
Masel et.[56]	2000	43	F	5	Tail	No	DP	wd,hk,a,n,abd	CT	439	NED	3.5
Thomason et al.[57]	2000	63	F	4	Tail	Yes	DP,S	wd,hk,a,wtls,d	CT	981	NED	6
Yek et al.[58]	2001	68	F	7	Tail		DP,S	wd,hk	CT		NED	5
Mortele et al.[59]	2001	75	F	7	Tail	No	DP	wd,hk,a,hc,d	MRI	3,486	NED	
Smith et al.[60]	2001	32	M	2	Tail	Yes	None	wd,hk	MRI	365		
Shorter et al.[61]	2002	20	F		Tail	No	DP	wd				
Ichimura et al.[62]	2003	50	F		Tail		DP,S	wd,hk,a,hc		7,200	NED	240
Drivas et al.[63]	2004	34	M	6	Head	No	PDD	wd,wtls,v		1,084		
Ghaferi et al. #1		74	M	14.5	Tail	Yes	DP,S	wd,hk,a,hc,d	CT	293	AWD	17
Ghaferi et al. #2		50	F	4.5	Tail	Yes	DP,S,LR,CB	wd,hk,v,a,hc	CT	770	DOD	96
Ghaferi et al. #3		66	M	5	Tail	Yes	DP,S,LR	wd,hk	CT	169	AWD	68
Ghaferi et al. #4		68	M	14	Head/body/tail	Yes	PDD,S	wd,hk,hc,wtls	CT	1,500	AWD	22

TSD = time since diagnosis, HG = hemigastrectomy, LR = liver resection, DP = distal pancreatectomy, S = splenectomy, PDD = pancreaticoduodenectomy, Enuc = enucleation, CB = celiac block, wd = watery diarrhea, hk = hypokalemia, a = achlorhydric, f = flushing, hc = hypercalcemic, d = dehydration, hch = hypochlorhydria, v = vomiting, ac = acidosis, DOD = dead of disease, AWD = alive with disease, NED = no evidence on disease

Radiologic features/modalities The imaging modality used to diagnose a pancreatic mass was reported in 23 of the 35 cases. The most common diagnostic study was CT (18/23, 78%). Magnetic resonance imaging and selective angiography were utilized in four cases and in one case, respectively. The primary tumor was always identified using one of the aforementioned modalities. Furthermore, metastatic disease to regional lymph nodes or liver was often diagnosed via imaging. Of the 35 case reports, 32 reported on the presence or absence of metastases, with 19 of the 32 (59%) reporting the presence of metastases, most commonly to the liver.

Site The site of primary disease in the pancreas was identified in all of the reported cases. The distribution of the primary tumors was as follows: 25 in the body and tail of the pancreas (72%) and 10 in the head of the pancreas (28%).

Size The primary tumors ranged in size from 2 to 10 cm in their greatest dimension, reported in 23 cases. The mean and median sizes were both 5 cm. Histologic confirmation of the tumor was reported in 18 cases with either routine hematoxylin and eosin staining or VIP immunohistochemical staining.

Treatment (surgery/none) Surgical intervention was reported in 30 of 35 cases (86%). The procedures included distal pancreatectomy (54%), pancreaticoduodenectomy (29%), splenectomy (43%), hemigastrectomy (6%), liver resection (6%), and tumor enucleation (3%).

Outcome The outcomes were reported with varying follow up periods. The mean follow up time was 40 months, with a median of 15 months. Outcome data were reported in 22 of the cases. Fifty nine percent of the patients were reported as alive with no evidence of disease, 23% had died of disease, and 18% were alive with disease.

Case Series

Summaries of the case series are tabulated in Table 2. Soga et al.[16] published the largest review of reported VIPoma cases including 241 patients found in an international literature search. The authors identified 179 patients with *pancreatic* VIPomas and compared the clinically reported data for this group of patients to the group diagnosed with *extrapancreatic* neurogenic tumors (n=48). They found statistically significant differences (p<0.05) between the two groups (pancreatic vs. extrapancreatic) in the rate of associated syndrome (84 vs. 96%), tumor size larger than 20 mm (79 vs. 100%), rate of metastases (56 vs. 29%), rate

Table 2 Summary of Case Series Reporting on VIPomas and our Institution's Cases

Case Series	Number of Cases	M:F	Mean Age (Range)	Mean Tumor Size (cm)	Mean VIP (pg/ml)	Presenting Symptoms (%)					Location of Tumor (%)			
						Diarrhea	Weight Loss	Dehydration	Hypokalemia	Flushing	Head	Body	Tail	Other
Soga et al.[16]	179	84:95	51 (15-82)	5.4		98	36		89	14	29	8	60	3
Smith et al.[17]	18fs	9:9	51 (23-74)	4.4	698	89	72	44	67	28	11	22	50	17
Peng et al.[18]	31	16:15	48 (26-73)	5.4	963	100	100	100		33	52	13	29	6
Nikou et al.[19]	11	7:4	53 (2-83)			100	45	45	81		18	9	55	18
Ghaferi et al.	4	3:1	65 (50-74)	9.5	683	100	50	25	100	0	0	25	75	0

of malignancy (64 vs. 33%), and rate of resection of the primary lesion (69 vs. 88%). The 5-year actuarial survival rate for patients with pancreatic VIPoma was found to be 69%. A significant difference existed between those with metastases at diagnosis vs. those without: 60% 5-year survival in patients with metastases vs. 94% 5-year survival in those without evidence of metastatic disease.

Smith et al.[17] presented the Mayo Clinic's 15-year experience with VIP-secreting islet cell tumors (Table 2). They reported on 18 patients with a mean age of 51 years (range 23–74) at presentation. There were equal numbers of male and female patients. As expected, secretory diarrhea was the most common presenting symptom in 89% of patients, and the most common location of the tumor was the tail of the pancreas (50%). The mean survival was 3.6 years, with the longest survival reaching 15 years.

Peng et al.[18] in 2004 presented a case report and clinical review of 31 cases of VIPoma in China (Table 2). They reported typical clinical manifestations, imaging features, surgical procedures, and pathologic findings. They found that the mean age of presentation was 48 years, with the mean size of the primary being 5.4 cm. The mean preoperative VIP level was 963 pg/ml (range 68–2,100), and the mean postoperative VIP value was 132 pg/ml (range 20–450).

In 2005, Nikou et al.[19] presented 11 patients with VIPoma (Table 2). Seven of the 11 patients were male, with an age range of 2 to 83 years (mean age 53.1 years). All patients presented with chronic secretory diarrhea that persisted despite fasting. Nine (81%) patients also presented with hypokalemia. Weight loss was observed in 45% of patients. Vasoactive intestinal polypeptide levels were three

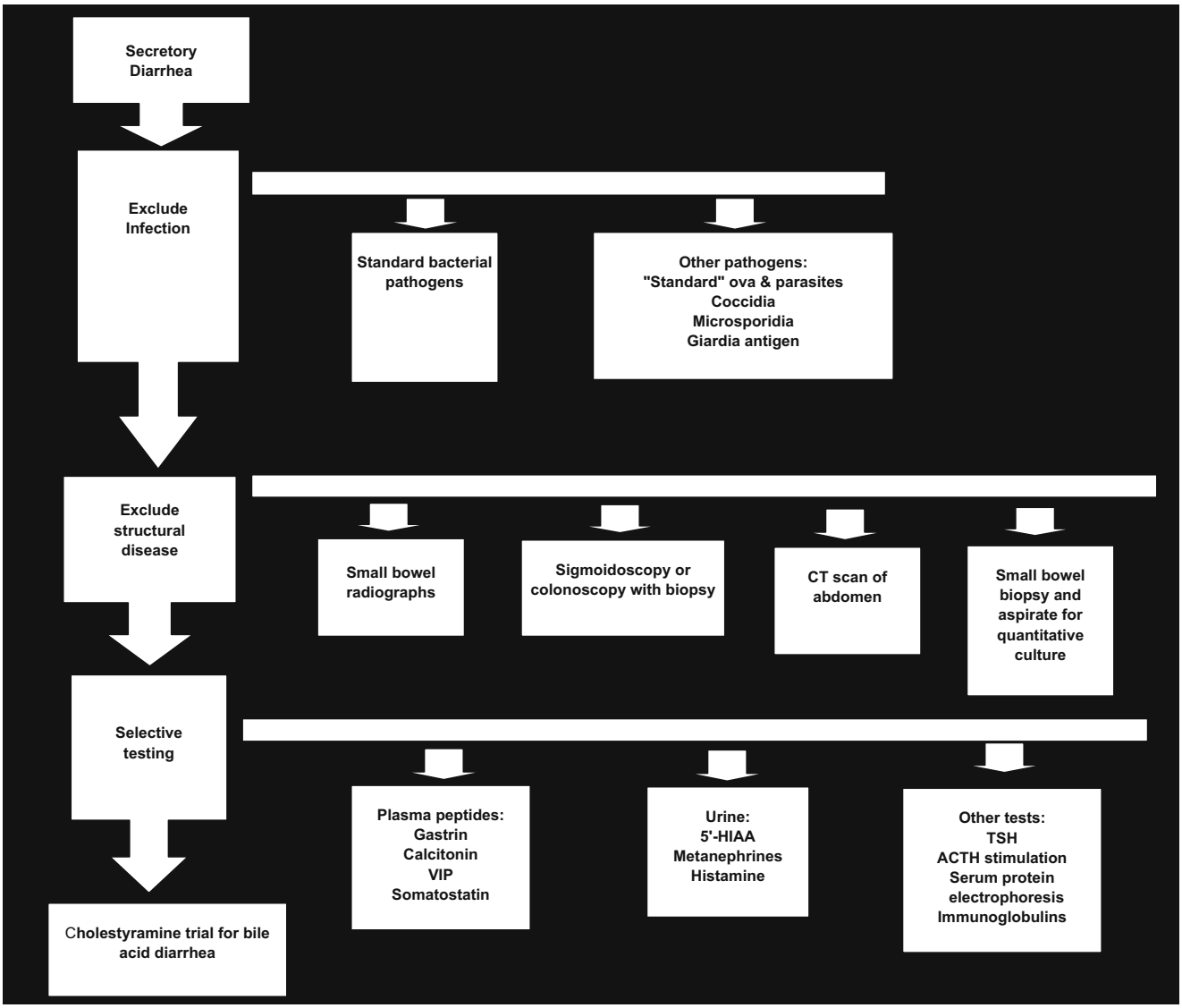

Figure 6 Algorithm for the identification of an etiology for secretory diarrhea. *5-HIAA*, 5-hydroxyindoleacetic acid; *TSH*, thyroid-stimulating hormone; *ACTH*, adrenocorticotropic hormone (adapted from Schiller[64]).

times normal in seven of the 11 patients and 10 times normal in the remaining four patients. Serum chromogranin A levels were elevated in all patients. Fifty four percent of lesions were detected by CT or MRI, whereas EUS or angiography detected 4/11 lesions (36%). Octreoscan detected the primary lesion in 10/11 (91%) and the metastases in 3/4 (75%). The primary lesion was located in the pancreatic tail in 6/11 (55%), the pancreatic body in 1/11 (9%), and the second portion of the duodenum in 2/11 (18%). A 2-year-old child included in the review had the primary tumor located in the retroperitoneum. Four patients had metastatic disease at the time of diagnosis. Sixty three percent of the patients underwent resection. At the time of the report, six patients were alive with no evidence of disease, two were alive with disease, and three had died of disease.

Discussion

VIPomas are rare tumors that often elude prompt diagnosis. As demonstrated by our review of the literature, nearly 100% of patients present with a primary complaint of watery diarrhea refractory to traditional medical management. Chronic diarrhea is defined as that which lasts at least 4 to 6 weeks; the prevalence of chronic diarrhea is estimated to approximate 3–5% of the US population.[20] Figure 6 depicts an algorithm for the workup of a patient with secretory diarrhea. Table 3 lists the causes of chronic watery diarrhea. The diarrhea associated with a neuroendocrine etiology, such as VIPoma, is typified by its persistence for 48 to 72 h after fasting, and by fecal volumes in excess of 6 to 8 l per day. The elevated serum levels of VIP result in all segments of the intestine secreting Na^+, K^+, Cl^-, and HCO_3^-, as well as water, thus accounting for the dehydration, hypokalemia, and acidosis associated with this syndrome. Other effects of excessive circulating VIP include inhibition of gastric acid secretion, bone resorption, glycogenolysis, and vasodilation. These effects lead, respectively, to the hypochlorhydria, hypercalcemia, hyperglycemia, and flushing often seen with these tumors.[21]

The VIPoma syndrome can be difficult to diagnose, as many other conditions can mimic its presentation. Laxative abuse and the Zollinger–Ellison syndrome have presentations similar to VIPoma. These entities can be differentiated by a careful medication history and by measuring serum gastrin and serum VIP and quantifying gastric acid production. Pancreatic islet cell tumors can secrete more than one hormone, as they may be comprised of more than one cell type. VIPomas have been noted to produce additional peptides including PP, calcitonin, gastrin, neurotensin, gastric inhibitory peptide, serotonin, glucagon, insulin, somatostatin, growth hormone-releasing hormone, and peptide histidine–methionine.[22] Two of the four patients at our institution had serum elevations of other peptides, and nearly 30% of the patients presented in the literature had multiple elevations.

Table 3 Differential Diagnoses of Chronic Watery Diarrhea

Diagnosis
Osmotic diarrhea
Mg^{2+}, PO_4^{3-}, SO_4^{2-} ingestion
Carbohydrate malabsorption
Secretory diarrhea
Laxative abuse (nonosmotic laxatives)
Congenital syndromes
Bacterial toxins
Ileal bile acid malabsorption
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Microscopic (lymphocytic and collagenous) colitis
Diverticulitis
Vasculitis
Drugs and poisons
Disordered motility
Postvagotomy diarrhea
Postsympathectomy diarrhea
Diabetic autonomic neuropathy
Hyperthyroidism
Irritable bowel syndrome
Neuroendocrine tumors
Gastrinoma
VIPoma
Somatostatinoma
Mastocytosis
Carcinoid syndrome
Medullary carcinoma of the thyroid
Neoplasia
Colon carcinoma
Intestinal lymphoma
Villous adenoma
Addison's disease
Epidemic secretory diarrhea
Idiopathic secretory diarrhea

Radiologic examination of patients serves as an important adjunct to clinical presentation and laboratory studies. Most pancreatic neuroendocrine tumors are highly vascular, making contrast-enhanced imaging very sensitive, with some groups reporting sensitivities as high as 92%.[23] Size of the lesion is an important factor in the ability of CT to detect a discrete mass. For tumors less than 1 cm, CT sensitivity is less than 10%. Because VIPomas are usually diagnosed at >3 cm, the sensitivity can approach 100%.[24] Our institutional experience with four cases yielded a mean tumor size of 9.5 cm, whereas the literature reports a mean of 5.2 cm. The role of MRI has gradually evolved, such that it is now an excellent technique for differentiating small

pancreatic tumors from surrounding normal pancreatic tissue. Thoeni and associates found the overall sensitivity of MR in detecting a pancreatic neoplasm in 20 patients suspected of having a malignancy to be 85% and the specificity to be 100%.[25] Somatostatin receptor scintigraphy relies on the relatively abundant expression of somatostatin receptors on these VIPomas. Eighty to 90% of VIPomas are somatostatin receptor-positive, making this scintigraphic study useful in most patients.

Histologically, the cellular patterns of VIPomas can be either solid, acinar, or trabecular with scant mitoses.[26] The pathologic evaluation of resected lesions serves as an important indicator of malignancy and prognosis. The only method of confirming malignancy is examination of local lymph nodes and suspicious distant sites of metastases, such as the liver. As reported in the literature, 60–80% of VIPomas are metastatic at the time of presentation.[22,27] Our institutional experience revealed that all four patients presented with local and/or distant metastases, with three patients having liver lesions in conjunction with local lymph node involvement and two patients having isolated local lymph node involvement.

Therapeutic intervention in VIPoma patients involves two interconnected pathways. Prior to the initiation of any curative or palliative therapy, the patient's potentially life-threatening electrolyte and volume status abnormalities must be corrected. Patients may require massive intravenous potassium replacement because the chronic gastrointestinal losses create a substantial potassium deficit. Once stabilized, the patient can be considered for surgical management. Over one-half of VIPomas have been reported as resectable, with a 10% "resectable for cure" rate.[28] Our institutional experience following surgical resection has yielded a 100% 1-year survival, with inadequate sample sizes to determine further survival rates. Two of our patients had complete resolution of their symptoms with surgical resection alone and are doing well at 17 and 22 months postoperatively. Another patient is alive and well 68 months postoperatively, following adjuvant octreotide therapy and radioablation of his liver lesions. Only one patient died 96 months after her resection, secondary to complications from diffuse metastatic disease. Our review of the literature found an 86% rate of resection. The range of follow up in that group was from 2 to 240 months, with a median of 15 months. Approximately 23% of the patients died of their disease from 12 to 52 months after the time of diagnosis or surgery.

Medical management with the synthetic octapeptide analog of somatostatin (octreotide) has proven useful in VIPoma patients with unresectable disease and/or metastases.[18,29] Octreotide inhibits hormone secretion by various neuroendocrine tumors (such as VIPomas and glucagonomas) and may very occasionally induce a reduction in the metastatic tumor burden.[30] Varying data exist about the quantitative reduction of tumor size and symptomatic relief. Oberg[31] reports a significant tumor response observed in less than 5% of patients but symptomatic response in 60% of patients. Similarly, Maton et al. reported that 83% of their patients with VIPomas had a good sustained symptomatic response to treatment, with fewer than 20% showing a reduction in tumor size.[32] Cho and Vinik evaluated tumor blood flow using angiography in eight patients with neuroendocrine tumors who were receiving octreotide. They found a marked decrease in blood flow to the tumor in two patients with gastrinomas and two patients with VIPomas, hypothesizing that there was either a direct vasoactive effect of the octreotide on the tumor blood supply or that this was a secondary effect from the decreased tumor hormonal secretion.[33]

Other forms of intervention exist for metastatic disease, including hepatic artery embolization, radiofrequency ablation, hepatic transplantation, radioactive octreotide, intravenous chemotherapy, alpha interferons, and cryotherapy. Each has been used in select cases. Despite the difficulty in diagnosing such a rare tumor, there are multiple treatment modalities available for VIPomas that provide meaningful, extended survival with excellent control of the watery diarrhea.

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Esophagospinal Fistula with Spondylodiscitis and Meningitis After Esophagectomy with Gastric Pull-Up

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Abstract Esophagectomy with gastric pull-up is a standard procedure for patients with esophageal cancer. Despite growing surgical experience, anastomotic leakage can still occur and cause significant morbidity. We report a case of anastomotic leakage with concomitant spondylodiscitis and describe the endoscopical appearance and closure of an unusual posterior fistula to the spine.

Keywords Esophageal cancer · Esophagectomy · Spondylodiscitis · Esophagospinal fistula

Case Report

A 64-year-old male patient presents with pain in the lower thoracic spine radiating to the flanks and both legs. Complaints started 5 weeks earlier, and physical therapy could not improve symptoms so far. In addition, he reports a loss of appetite due to nausea and fever since 3 days.

The patient formerly consumed significant amounts of nicotine and alcohol and suffers from chronic bronchitis since then. Eighteen months before the current presentation, he had diagnosis of a squamous cell carcinoma in the middle part of the esophagus (pT3, N_0, M_0; G3). He received neoadjuvant radiochemotherapy before transthoracic esophagectomy with gastric pull-up at an outward hospital. Postoperative course was uneventful, and the patient denies dysphagia since then.

On clinical examination, the patient was febrile with 39.2°C; palpation of the kidneys was indolent, but the thoracic spine was painful. Neurological examination excluded menigism but revealed weakness of both legs while sensibility and perception were unaltered. Laboratory tests showed systemic inflammation with elevated C-reactive protein of 8.35 mg/dl (normal <0.5 mg/dl) and leukocytosis of 11.2/nl (<10.0). A chest radiograph and abdominal ultrasound did not find metastases or inflammatory foci, but the cerebrospinal fluid revealed pleocytosis with 1,238 leukocytes/μl (93% neutrophils), elevated protein (22.49 g/l), and lactate (9.4 mmol/l). Magnetic resonance imaging scan confirmed the diagnosis of a spinal meningitis and demonstrated spondylodiscitis of vertebral bodies Th3 and Th4 as well as a small paravertebral abscess. Blood cultures approved streptococcal infection.

Esophagogastroduodenoscopy showed a defect in the posterior wall of the esophagus at the anastomosis (Fig. 1), and air bubbles were rising from the orifice. A catheter was inserted into the luminal opening, and contrast medium was applied to trace the suspected fistula. Fluoroscopy revealed an esophagospinal fistula with accumulation of contrast media in the intervertebral disc Th3/Th4 (Fig. 2). The fistula was closed by injection of fibrin sealant into the channel and application of two endoclips. A gastrografin swallow and endoscopic follow-up examinations documented the effective sealing of the fistula without the need for further interventions. Antibiotic treatment could eradicate spondylodiscitis without the requirement for drainage or surgery.

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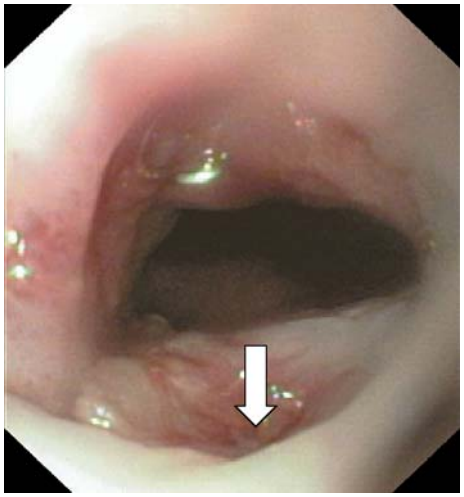

Figure 1 Luminal opening of the fistula (*arrow*) in the posterior wall of the esophagus proximal to the anastomosis.

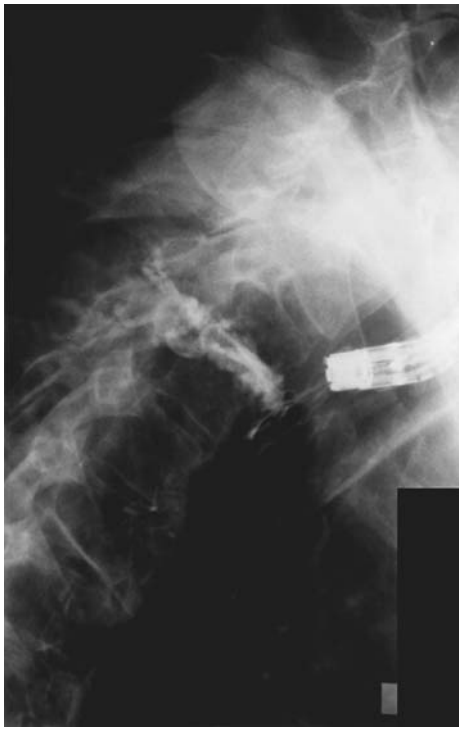

Figure 2 Verification of the esophagospinal fistula with accumulation of contrast media in the intervertebral disc Th3/Th4 after insertion of a catheter into the luminal opening via the endoscope in the esophagus.

Discussion

Anastomotic leakage after esophageal surgery has an incidence between 5 and 30%. Approximately 13% of patients develop cervical leakage, but in most cases, a complete healing of the defect can be achieved.[1] However, in rare cases, cervical anastomotic leaks can lead to the formation of anterior esophagotracheal fistulas with high morbidity and mortality. Enterospinal fistulas have been reported spontaneously in Crohn's disease[2] and as complication of anastomotic insufficiency after large bowel surgery.[3] Cervical osteomyelitis and abscess formation have been described after placement of a metal stent into the esophagus[4] but seems to be very uncommon postoperative sequelae after esophagectomy. A larger series of 842 patients with cervical esophagogastric anastomosis revealed three cases of cervical osteomyelitis (i.e., 0.35%) resulting in a lethal course in two patients.[5] In neither case, a postoperative barium swallow detected a leak of fistula. In our case, endoscopy demonstrated a luminal opening at the posterior wall of the esophagus, and fistulography confirmed the formation of a fistula to the spine resulting in spondylodiscitis with meningitis.

The area of the cervical anastomosis is most vulnerable for ischemia and fistula formation because it is the farthest from the right gastric and gastroepiploic arteries that nourish the stomach.[5] Necrosis or fistula formation is associated with serious morbidity and usually requires surgical reintervention; however, in our case, the luminal opening could be effectively closed by application of clips and fibrin sealant without major debridement or dissectomy of the defect.

Therefore, the endoscopical closure of rare esophagospinal fistulas in combination with systemic antibiosis may be a sufficient treatment for cervical anastomotic leakage and may replace surgical reoperation in single cases.

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Letter to the Editor

Michael G. Sarr

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Dear Editor:

I read the article by Safatle-Ribeiro et al.[1] from the University of Sao Paulo School of Medicine in Sao Paulo, Brazil.

I am disappointed to see that they have overlooked several previous "classic" articles on this subject. The first paper was by Flickinger et al.[2] in 1985 and another article by Strodel et al.[3] in 1984. The former quite clearly describes the chronic gastritis described by Safatle-Ribeiro et al. In fairness to Flickinger et al., I think this needs to be pointed out.

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Commentary Regarding Flancbaum L, Belsley S, Drake V, Colarusso T, Tayler E. Preoperative Nutritional Status of Patients Undergoing Roux-en-Y Gastric Bypass for Morbid Obesity. J Gastrointest Surg. 2006 10(7):1033–7

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Nutritional deficiencies are a known complication following Bariatric procedures, especially after malabsorptive procedures, such as Roux-en-Y gastric bypass and biliopancreatic diversion, but may occur after restrictive procedures, as after any gastrointestinal surgery.[1–6] Various nutritional deficiencies were described after these procedures.[1–6] The gravest presentations were described in accordance with thiamine deficiency leading to severe neurological pathology.[1,2,6] A study by Flancbaum and coworkers[7], which was published in 2006, retrospectively analyzed the preoperative values of various nutrients, including thiamine, in patients undergoing bariatric surgery. Twenty-nine percent of the patients had preoperative thiamine deficiency. In their study, the authors stated that they were the first to describe preoperative thiamine deficiency in bariatric patients. However, Flancbaum's study only confirmed what we have presented at the 22nd Annual Meeting of the American Society for Bariatric Surgery on June 2005, and published in 2005[8], in which we demonstrated that, out of 303 morbidly obese patients who were scheduled for bariatric surgery, 47 patients (15.5%) presented with low preoperative thiamine levels. In our study, none of the patients had preoperative or postoperative clinical manifestations of thiamine deficiency.

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In our opinion, the findings of both studies cannot be ignored; in patients with marginal thiamine levels, deficiency may be facilitated by increased demands due to the surgical stress, rapid weight loss, unbalanced diet, and loss of absorptive area after surgery, and may result in neurological and cardiac deterioration.[1,2,6] The standard of care should include preoperative thiamine screening and perioperative replacement. Most importantly, prolonged vomiting should be an indication for empiric thiamine treatment, even without biochemical deficiency. We would like to congratulate Flancbaum and coworkers for confirming our initial findings.

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What to Expect in the Excluded Stomach Mucosa After Vertical Banded Roux-en-Y Gastric Bypass for Morbid Obesity

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Dear Editor:

We would like to thank Dr Sarr for his interest in our article on double balloon endoscopy and its use in obese patients who underwent gastric bypass.[1] This is a timely subject due to the increased frequency of utilization of this surgical technique and because of the difficulty in endoscopic examination of the excluded stomach.

Although gastric bypass has been in use since late seventies, vertical banded Roux-en-Y gastric bypass using a long limb has become a common and gold standard procedure in the nineties. Double balloon endoscopy is a new technique that allows the complete endoscopic examination of the excluded tract.

The double balloon endoscope and the overtube pass through the esophagus (40 cm), proximal gastric pouch (5 cm), Roux-en-Y jejunum loop (100 to 150 cm), biliopancreatic jejunal limb (50 to 75 cm to the ligament of Treitz) and duodenum (20 cm), plus the excluded stomach itself (10–15 cm), adding up to a total scope intubation in the range of 2–3 m.

Since *Helicobacter pylori* colonization in the excluded stomach and the natural history of this colonization has not been evaluated after surgical treatment of obese patients, the aim of our investigation was to analyze the mucosal alterations and especially the presence of *H. pylori* in the excluded stomach and in the gastric stump epithelium (functional pouch) after gastric bypass for morbid obesity.[1]

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We did not intend to overlook any of other "classic" articles. In our initial paper on endoscopic assessment of the excluded stomach utilizing a double balloon endoscope[2], we have appropriately referenced Dr. Flickinger's research on retrograde endoscopy of the bypassed stomach using a fiber-optic pediatric colonofiberscope.[3] They reported the use of the colonoscope to perform endoscopic examination in a short Roux-en-Y limb with a success rate of 66.2% (45/68) in examined patients. The Greenville surgical technique utilized in their patients had a short efferent limb of 25 to 40 cm in length, and the Roux-en-Y configuration was performed with a side-to-side stapled jejunojejunostomy 10 to 15 cm from the ligament of Treitz.[3,4] They also detected bile staining in the distal stomach and gastritis and metaplasia in the proximal pouch and in the distal stomach.

Strodel et al.[5] examined two cases of Roux-en-Y gastric bypass. They could reach the distal excluded stomach only during exploratory laparotomy with passage of an intraoperative endoscope assisted by the surgeon in one patient. They stated that exclusive of intraoperative examination, the excluded stomach and proximal duodenum could not be examined endoscopically using standard techniques. In that patient, the pylorus appeared to be scarred, and stenotic and multiple superficial ulcerations could be detected in the excluded distal stomach.

Therefore, to our knowledge, we have reported for the first time the utility of double balloon endoscopy and documented the *H. pylori* status in the excluded stomach, achievements that we believe are substantial and should be brought to the attention of those caring for this patient population.

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Letter to the Editors

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Dear Editors,

We write to acknowledge the inadvertent re-publication of a portion of the mRNA expression gel in Figure 1 of the paper entitled "The Pathogenesis of Barrett's Esophagus: Secondary Bile Acids Upregulate Intestinal Differentiation Factor CDX2 Expression in Esophageal Cells" published in the Journal of Gastrointestinal Surgery in July of 2007.

A mosaic of this experiment and an experiment involving bile-induced stimulation of the MUC2 gene had been previously published in our paper that appeared in the Archives of Surgery in June of 2007. While our CDX2 expression experiments had been repeated over the course of the data collection for the relative papers, the gels regarding CDX2 and B-Actin from each of these figures were generated from the same experiment. This was an inadvertent oversight, which was unintentional and for which the authors apologize. The remainder of the data and experiments from the two publications were unique and disparate in time and we believe investigated distinct hypotheses. Please accept our most sincere regrets for the inadvertent duplicate publication of the gel data.

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