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EDITORIAL

Tribute to John L. Cameron, M.D.

Jeffrey B. Matthews · Charles J. Yeo

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Dr. John L. Cameron has been involved with every issue of the *Journal of Gastrointestinal Surgery* since it was founded in 1997. Together with Co-Editor Dr. Keith A. Kelly (now emeritus), Dr. Cameron brought the journal from a quarterly publication to one that is published monthly and now receives over 1,200 submissions annually. This month, as he transitions from his role as Editor in Chief, Dr. Cameron, along with Dr. Kelly, will be listed on our new masthead as our Founding Editors. We, the new co-editors of the journal, would like to recognize and honor Dr. Cameron's remarkable achievements.

Dr. Cameron was born and raised in Michigan. He received his undergraduate degree from Harvard University in 1958 and his medical degree from the Johns Hopkins University School of Medicine in 1962. After completing his medical studies, Dr. Cameron completed all of his surgical training at the Johns Hopkins Hospital. In 1971, he was appointed Assistant Professor of Surgery at Johns Hopkins. He was promoted to Associate Professor in 1974 and to full Professor in 1978. He was the recipient of numerous NIH grants studying gastrointestinal physiology and focusing on pancreatitis. In 1984, he was named Surgeon-in-Chief of the Johns Hopkins Hospital and Chairman of the Department of Surgery in the Johns Hopkins University School of Medicine. After a 19-year tenure, in 2003, Dr. Cameron stepped down from his position as Surgeon-in-Chief to assume the position of the Alfred Blalock Distinguished Service Professor. Dr. Cameron remains active as a clinical surgeon, operating 5 days a week, as a teacher, and as an investigator. His career at Johns Hopkins now spans a 53-year period.

Throughout his career, Dr. Cameron's interests have primarily been focused in the field of alimentary tract surgery. He has made many contributions to the understanding of the pathophysiology and management of a variety of benign and malignant pancreatic diseases. He was an early investigator in the field of acute pancreatitis, and his name is most often associated with the Whipple procedure, a complex operation used to treat a variety of pancreatic diseases, including pancreatic cancer. He has performed more of these Whipple operations than any other surgeon in the world. Dr. Cameron has been a member of many of the most important surgical associations and societies in the USA and has served as the President of the Halsted Society, the Society for Surgery of the Alimentary Tract, the Society for Clinical Surgery, the Society for Surgical Chairs, the Southern Surgical Association, the American Surgical Association, and the American College of Surgeons.

Dr. Cameron has published well over 450 articles and over 100 book chapters, and he is the editor of 20 books. He has been on the editorial boards of many journals and still serves as the editor of *Advances of Surgery* and co-editor of *Current Surgical Therapy* (now in its 10th edition).

Under Dr. Cameron's supervision, the *Journal of Gastrointestinal Surgery* has become one of the premier international journals in the field of alimentary tract surgery. The journal's impact factor has continued to rise, and its editorial board now spans many continents and includes

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prominent alimentary tract surgeons from around the world. Dr. Cameron has proven to be a remarkable mentor to many and, particularly, to us, the rising new co-editors of the *Journal of Gastrointestinal Surgery.* We appreciate the guidance he has given us over the last 4 years as associate co-editors, and we hope that we will be able to continue to call on him for advice. We are grateful for the energy and leadership that Drs. Cameron and Kelly provided during the time that this journal was in its early days. We only hope that we can carry on their tradition and continue to strengthen the journal and its affiliation with the Society for Surgery of the Alimentary Tract.

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SSAT CONSENSUS STATEMENT

Looking Ahead: The SSAT Strategic Plan for the Next Decade

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Abstract The Society for Surgery of the Alimentary Tract's (SSAT) mission is to advance the science and practice of surgery in the treatment of digestive disease. An essential core value of the SSAT is multidisciplinary collaboration with both its sister societies in the Digestive Disease Week (DDW) Council and other surgical societies in Gastrointestinal Surgery. In order to achieve the society's goals, the strategic plan rests on the society's values of interdisciplinary collaboration, scholarship, education, and discovery. The strategic plan also creates a meritocracy system to foster the development of future leaders for both the SSAT and the broader house of surgery. In the short term, this plan will:

- Re-organize committee structure and reporting responsibilities;
- Clarify committee goals and deliverables;
- Facilitate member participation in the committees and governance of the society;
- Enhance member services by utilizing enhanced communication strategies;
- Accelerate efforts to meet the Maintenance of Certification needs of the membership;
- Re-focus the SSAT's energy on Quality and Outcome Assessment of GI surgery;
- Clarify and standardize the methodology for allocating funds for new projects.

Over the course of the next few years, the SSAT will:

- Develop a financial model that increases revenue to support the expanded tasks the society intends to undertake;
- Play an active role in developing the evolving training paradigms for gastrointestinal surgeons through the continuum from residency, fellowship, and early mentored practice;
- Continue to support development of surgeon scientists through Career Development Award;
- Enhance relationship with the SSAT Foundation;
- Continue to improve the experience of members attending DDW;
- Develop surgeons interested in public policy to be leaders at a national level.

The strategic plan is ambitious, and the current leadership realizes that all the tasks and objectives cannot be accomplished in 1 year. There is much to do in order to keep the SSAT the premier professional society for gastrointestinal surgery. Changes in the external environment may require modifications of the priorities or the plan itself in the coming years. Implicit in this plan is the need for annual review by the Board of Trustees at the May Board Meeting so that modifications can be made as the world around us changes.

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Keywords Society for Alimentary Tract · SSAT · Strategic Plan

Introduction

During the annual SSAT Board meeting in May 2010, the Trustees determined that it was time to review the direction that the SSAT was heading and map out a clear course for the future of the organization. In October 2010, a strategic retreat was held to begin this task. Many issues and solutions were discussed by the group of 30 key SSAT leaders—past, present, and future. In simplest terms, the retreat focused on the challenges facing the SSAT, the core strengths and values of the organization, and the opportunities to help shape the future of Gastrointestinal Surgery. This document is intended to be a roadmap for the SSAT as it moves forward.

Mission, Vision, and Values

Mission (what the SSAT does):

> The SSAT is committed to advancing the science and practice of surgery in the treatment of digestive disease.

Vision (what the SSAT will be):

> The SSAT will provide leadership in setting the standards for gastrointestinal surgery and interdisciplinary management of digestive disease, in North America and around the world.

Values (for what the SSAT stands):

> Education
> Scholarship
> Discovery and Innovation
> Quality Clinical Care
> Leadership
> Meritocracy
> Interdisciplinary Collaboration

Process for Implementing the Strategic Plan

The strategic plan will be reviewed at each Board of Trustees meeting, and all new or ongoing projects will be evaluated for fit within the Mission, Vision, Values, and Plan. Since the plan calls for an increase in the number of committees and the scope of their work, a transparent system for participation by SSAT members in the committees as well as promotion to positions of greater responsibility in the organization is outlined in this document. A primary goal of the strategic plan is to maximize opportunities for members to participate in the activities of the SSAT, identify future leaders of the organization, and promote people on the basis of the quality of their contributions to the organization's mission. Committee chairs will be mentored by a senior member of the executive committee or Board of Trustees and the chairs' performance evaluated annually to ensure that the resources and leadership needed to accomplish the SSAT's goals are sufficient. Each committee, led by their chairperson, will refine the goals and priorities set out for them in this plan and establish deliverables with appropriate timeframes. SSAT funds will be allocated based on these priorities. New requests with budgetary implications will be evaluated first by the Finance Committee and then referred to the Board of Trustees for approval. All committee chairs will be asked to present a biannual report to the SSAT Board of Trustees.

Achieving the goals set out in this plan will require enhanced communication from the leadership to convey the scope of the changes to the organizational structure and culture as detailed in the plan and also the mechanism for implementing these changes. While the strategic plan will be posted on the SSAT web page, effective communication to the membership will also require several letters from the President and Chairman of the Board, establishment and utilization of social media, presentations at the 2011 Digestive Disease Week (DDW), and face-to-face networking with the membership by the society's leaders.

In order to implement many of the changes called for in the strategic plan, it is necessary to revise the committee structure of the SSAT so that form can follow function. Appendix 1 details the new committee structure and committee tasks. Table 1 contrasts the former committee structure with the new committees in bold font and the former committees in regular font. The prior organizational structure was felt to be too horizontal for the revamped committees to function in a coordinated fashion. Therefore, the committees have been clustered based on key activities into the four working groups of Education, Research, Members Services/Policy, and Administration.

Education Working Group	Research Working Group	Member Services/Policy Working Group	Administration Working Group
Program Committee	Research Committee	Member Services Committee	Board of Trustees
Program Subcommittees	Health Care Quality and Outcomes	Communications Committee	Executive Committee
Resident Education		Public Policy & Advocacy Committee	Finance Committee
Continuing Education		International Committee	Nominating Committee
Maintenance of Certification			
Advanced training Committee			

Table 1 SSAT committee structure now and before

New Committee	Former Committee
Research	Research
Member Services	Membership
Communications Committee	Publications
Public Policy & Advocacy	Public Policy
Health Care Quality and Outcomes	Patient Care
Resident Education	Education
Continuing Education	Education
Maintenance of Certification (MOC)	n/a
Advanced training Committee	n/a
Bylaws Committee (Ad Hoc)	n/a

Organizationally, the Administration working group will oversee the other three working groups. The Education, Research, and Member Services/Policy Working Groups will be comprised of the chairs of that working group's committees, as well as designated senior leadership from the executive committee or Board Trustees who will provide executive oversight. Oversight of these groups will be provided as follows: The Education working group will be overseen by the Secretary, The Administration working group will be overseen by the Chair of the Board of Trustees, The Research working group and the Member Services/Policy working group will each be overseen by a member of the Board of Trustees serving their second 3-year term on the Board. The senior trustees responsible for oversight of the working groups will be appointed by the President.

In the past all committee members have been appointed by The President. Going forward, however, most committee positions will be filled by members volunteering and signing up through the SSAT webpage. This is intended to enhance participation by the membership and open up active roles in the society to members who may not have been from the same institution as the top leadership. For most committees the President will appoint the committee chair and co-chair and up to 20% of the committee members. The remaining positions will be filled directly by members who sign up via the web. Certain small committees such as the nominating committee and the GI training committee (or other ad hoc committees created by the Board in response to a new or acute need) will be filled by appointment only. Nonetheless the strategic plan's clear intent is to maximize participation by the SSAT membership in the committee process by establishing this open sign up process. The committee chairs will provide an annual assessment of each committee member's participation to the senior leadership. Reappointment and consideration for subsequent leadership positions will be based on this information.

There were nearly 50 action items identified at the strategic retreat. It is the feeling of both the SSAT leadership and the consultants who facilitated the retreat that the society can process between four and six initiatives per year. Therefore the initiatives need to be prioritized. This prioritization should be reviewed annually as the external environment changes. For each initiative the tactics, direct and indirect costs (if applicable), business plans, etc. should be confirmed before they are officially launched.

The short-term priorities for 2011 are:

1. The membership committee will develop, administer, and present an evaluation of the member needs survey results to the board in May 2011
2. The SSAT website will be revised making it a major unifying educational resource not only for our members but for all professional and lay people interested in the current art and science of GI surgical practice. The Board of Trustees intends to make a significant financial commitment to expedite achievement of this goal
3. Restructure Committees to better serve the Mission of the SSAT
    a. Bylaws revision via the Bylaws subcommittee recommendations
    b. Create a Committee Handbook
    c. Change the Committee appointment process
4. Intensive effort to provide Maintenance of Certification (MOC) content to membership and create a vehicle for members to fulfill MOC Part IV requirements
5. Establish and energize the Health Care Quality and Outcomes Committee

The long-term priorities are:

1. Education
    - Annual meeting
    - Maintenance of Certification
    - Resident education day
    - Lead efforts in GI Surgery training both during and after surgical residency
2. Research
    - Continue present commitments to fund research without adding more Career Development Awards
    - Strive to be the premier venue for presentation of translational research work pertinent to gastrointestinal surgery
    - Be a home for high-quality outcomes research
3. Public Policy
    - Inform policy makers, healthcare providers, and patients about issues impacting the delivery of quality GI Surgical Care

- Engage in healthcare politics
- Create future leaders who will influence public policy
- Focus on quality and outcome metrics that are valid for GI surgery

Goal Areas

1. MEMBER SERVICES

Objective

Serve as the premier member resource center for Digestive Disease

Initiatives:

a. Expand the role of SSAT in Maintenance of Certification
Tactics:

- Task the MOC Committee with creating a plan to address MOC issues for our members. The plan will include an overall objective, lines of activity, and key needs in the MOC project(s). Timelines for an execution of the plan and points of accountability will be determined in the planning phase of the project. Identify what other competing MOC products exist and at what price points, and examine alternate, more cost-effective platforms for delivering MOC as well as potential collaborative and cost-sharing efforts with sister societies
- Further task the MOC Committee with determining the feasibility of CME sponsorship for internet enduring materials versus pursuing self-accreditation
- Report to the Board of Trustees with a preliminary outline and benchmarks by May 2011
- Flesh out the "SSAT road show" concept that would address MOC Part IV via case reviews by expert panels

b. Conduct a comprehensive member needs assessment to drive SSAT programs and services
Tactics:

- Identify names of consultants who could advise the SSAT, help establish protocols, coordinate question development and mailings/emails, tabulate/analyze responses, and prepare a report. Request proposals from consultants; interview no more than three consultants and hire one by March 2011
- Identify a major Task Force comprised of a diverse and representative group of members to participate in the development of the assessment project. Identify a strong Chair of the Task Force who will help drive the agenda and get it done. Appoint the Chair by the end of 2010 and finalize the Task Force by January 2011
- First report to the Board of Trustees on preliminary work and final timeline by February 2011
- Explore various data collection methodologies, including conducting a baseline survey followed by members with those who do not participate/attend DDW
- Present survey results to Board of Trustees by May 2011

c. Explore the opportunities for SSAT at the "DDW Oasis"
Tactics:

- With the Program Committee, work with DDW-Administration to identify new interdisciplinary programs and communication opportunities that the SSAT could offer within the Oasis—and whether those opportunities are something on which the SSAT could take the lead
- Prepare an outline of ideas and a white paper detailing the pros and cons of—and a budget for—any SSAT offerings

2. FINANCE

Objective:

Ensure financial processes are defined and resources appropriately allocated to meet the member needs

Initiatives:

a. Define the role, structure, policies, and procedures of the Finance Committee in managing the fiscal resources of the SSAT (Reserve Policy, Investment Guidelines, Business Plan templates, etc.)
Tactics:

- Schedule a series of conference calls with the Finance Committee to develop, review, and modify a white paper outlining reserve options and a fiscal policy manual, as well as a business plan template. Present a progress report to the Board of Trustees by February 2011 and a final paper by May 2011

Suggestions for Finance Committee white paper

Reserve Options:

- The SSAT should maintain 1-year operating reserves at all times in a Permanent Fund that must grow by the Cost of Living (COL) *every* year. If the interest and growth does not equal the COL increase, then excess revenue over expenses from the operating fund must be transferred to the Permanent Fund to make up the difference. If the interest/growth outpaces the COL increase, excess revenue can be transferred for research and development.
- Once a 1-year reserve has been accumulated, reserve dollars over that amount should go to a Research & Development (R&D) Fund for new projects. The Board of Trustees will approve the release of R&D dollars through the Board of Trustees to Committees, Task Forces, etc. for new programs provided a Committees/Task Force has presented a business plan for the use of the money. The Business Plan pro forma should include the following:
  - Name of Project/Proposal
  - Relation to Mission, Vision and Values, and Goal Areas
  - Pros and Cons: the reasons to undertake the project and an equal number of reasons the project could fail or be unsuccessful
  - Budget: the direct and indirect costs associated with the project; indirect costs should include estimates of additional staff time required
  - Timelines: the start-to-finish time for the work and specific benchmarks to evaluate the project
  - Point(s) of Accountability: the committee, staff, task force, or other who is responsible for all aspects of the project
  - ROI: if the project includes an opportunity for profit, a business plan, out to 5 years, will be requested
  - Approval: date

Operating Budget and Financial Reports: The annual budget for the SSAT must be approved at least 60 days prior to the start of the calendar/fiscal year. The Finance Committee with staff must prepare the document for approval. Quarterly financial reports are sent to the Chair of the Board, the President, and the Treasurer. Monthly statements will be reviewed by the Treasurer. More frequent review will ensure project accountability

b. Work with appropriate SSAT Committees to increase SSAT net revenue by 25% by December 2012
Tactics

- With Committee input, staff should identify all potential revenue sources for SSAT by May 2011 with a priority ranking of where increases could be realized—e.g., member dues, ticketed SSAT course fees at DDW, new CME programs and course offerings outside of DDW, MOC, new publications (the SSAT's best from DDW in a monograph publication), publishing agreements, international meeting opportunities, etc. The white paper should develop revenue potential for each area and outline ways to make it happen
- Present findings at a meeting of the Executive Committee and prioritize all items from 1 (real) to 4 (fantasy), and then concentrate on realistic opportunities. Seek Executive Committee input on the creation of a Task Force to help finalize plans and an agenda. Present to the Board of Trustees by May 2011
- Charge the Committees with developing business plans for each realistic, high-priority opportunity, and task them to begin to achieve results within 1 year. These efforts will require significant (and potentially additional) staff support

3. ORGANIZATIONAL STRUCTURE AND IDENTITY

Objective:

Assure that the organizational structure is effective, efficient and accountable

Initiatives:

a. Revise the Bylaws and create policies and procedures to govern the operations of the SSAT
Tactics:

- Create a Policy Manual. Present to the Board of Trustees by May 2011. The Table of Contents for such a Policy Manual could include the following:
  - Mission Statement
  - Vision Statement
  - Values
  - Board of Trustees—Roles and Responsibilities
  - Board Priorities
  - Board Meetings—Schedule, Agenda, Protocols
  - Agenda Book Guidelines—Consent Agenda, Action Agenda and Information Agenda, and Board minutes
  - Parliamentary Procedure
  - Budget development and approval
  - Financial reporting

- Investment guidelines (see above for policy)
- SSAT Travel and Reimbursement guidelines
- Insurance
- Conflict of Interest Policy
- Committee Appointment Policy
- Disciplinary Hearing Policy
- Legal Activity Guidelines
- Endorsement Policy/Guidelines
- SSAT Crisis Communication Plan
- Use of SSAT letterhead and logo
- SSAT Liaison Program
- SSAT staff

- Appoint a Task Force to revise the Bylaws with staff assistance. Present to the Board of Trustees by May 2011. Disseminate amended Bylaws to membership by April 2011. Vote to affirm at Annual Meeting in May 2011
- Create a Committee Handbook for all Committee work. Present to the Board of Trustees by June 2011. The Table of Contents for such a Committee Handbook could include the following:
  - SSAT Committees and their Roles
  - Committee Overview
  - Appointment and Tenure Policy
  - Committee Work Groups
  - Types of Committees defined—Standing, Ad hoc, Task forces, etc.
  - Committee and Board organizations chart
  - Work Group objectives and listing of Committees and their charges
  - Committee business plans and reporting format on projects, etc.

b. Restructure the Board of Trustees Meeting and the Committees to be consistent with the mission
Tactics:

- The revision of the bylaws and creation of policies and procedures to govern the operations of the SSAT should take into account the SSAT's mission statement, "Advancing the science and practice of surgery in the treatment of digestive disease"
- Add dedicated time for Committees to meet at DDW, prior to the Board of Trustees meeting and request that committee chairs present a report at each board meeting

c. Identify strategic alliances that will effectively serve the needs of members
Tactics:

- Develop criteria for identifying alliances and partnerships that offer value to SSAT members and leaders
- Generate a list of potential areas for collaboration, including MOC, advanced training, advocacy, scientific programming, and patient care guidelines
- Approach other DDW and surgical societies regarding the possibility of providing updates on each other's initiatives to assist with identifying collaborative areas

d. Create a program that identifies and develops future leaders in SSAT activities. The SSAT should be a meritocracy where accomplished Committee members can rise to higher leadership positions
Tactics:

- Allow open, self-nomination for each committee's open slots
- Committee Chairs will evaluate members for attendance, participation, and utility, and recommend to the Executive Committee those whose terms should be extended

e. Explore the opportunity to develop an advanced GI training strategy
Tactics:

- Appoint an Ad Hoc Committee to study and make recommendations on the training of the advanced GI surgeon. Work with the Fellowship Council (FC), the American Board of Surgery (ABS), and other GI specialty societies (e.g., SAGES, AHPBA, ASBMS, ASCRS) to be inclusive of their educational interests
- Increase the SSAT's profile and recognition as the leader in designing and implementing the "next generation" in advanced GI surgery training programs from residency through mentored practice

f. Explore opportunities to increase collaboration with the Foundation
Tactics:

- Work with the Foundation Board to develop a strategic plan similar to the SSAT's

Appendix 1: SSAT Committee Structure and Tasks (Reflects the Initiatives and Tactics in the Strategic Plan)

1. Administrative working group
   Board of Trustees
   Executive Committee
   Nominating Committee
   Finance Committee

GOAL: Ensure the financial processes are defined and resources appropriately allocated to meet the needs of the membership and the society

TASKS:

a. Assist other committees in creation of buisness plans when funds are needed to accomplish committee tasks and programs
b. Define the role, structure, policies, and procedures of the Finance Committee in managing the fiscal resources of the SSAT (Reserve Policy, Investment Guidelines, Business Plan templates, etc.)—Write the White Paper as proposed in the Strategic Plan
c. Work with appropriate SSAT Committees to increase SSAT net revenue by 25% by December 2012

2. Education Working Group

Program Committee

GOAL: The Program Committee will develop the highest quality program for the annual meeting

TASKS

a. Define appropriate subcommittees for abstract review and selection
b. Develop program for annual meeting based on current environment and feedback from prior meetings
c. Coordinate program with other DDW Societies

Continuing Education Committee

GOAL: The Continuing Education Committee will play a pivotal role in all of the Society's educational activities

TASKS

a. Work with Program Committee to coordinate Joint Symposia with other Societies both at DDW and other meetings (AHPBA, ASCRS, ISDS, SAGES, SSO, etc.)
b. Identify new CME opportunities
c. Develop content for MOC committee—especially Part II
d. Advise Board and program committee re ACCME guidelines
e. Create NEW non-meeting Learning Moments
»Podcasts with Experts, Specialty Blogs
f. Recommend the recipients of the annual Fischer International and DeMeester US/Canada travelling fellowship awards to the Board of Trustees

Resident Education

GOAL: To Facilitate resident participation in SSAT and DDW activities

TASKS

a. Enhance Friday Resident and Fellows Research Conference
b. Develop sessions at meeting that are targeted at residents such as "How to Assess a Job/Fellowship"
c. Seek out Resident members (two) to serve on the committee
»Work with members services to enhance resident member category of SSAT
d. Work closely with Communications committee to ensure that appropriate media are used to enhance access to SSAT by surgical residents

Maintenance of Certification

- Task the MOC Committee with outlining a plan to address MOC issues that includes an overall objective, lines of activity, and key needs in the MOC project(s), as well as timelines for achievement and points of accountability. Identify what other competing MOC products exist and at what price points, and examine alternate, more cost-effective platforms for delivering MOC as well as potential collaborative and cost-sharing efforts with sister societies
- Further task the MOC Committee with determining the feasibility of joint CME sponsorship for internet enduring materials versus pursuing self-accreditation
- Report to the Board of Trustees with a preliminary outline and benchmarks by February 2011
- Flesh out the SSAT road show concept that would address MOC Part IV via case reviews by expert panels.
- Advise re MOC course cycle for Part II MOC
- Develop product for Part IV MOC

GI Surgery Training Committee (Ad Hoc)

GOAL: To explore the opportunities for GI surgical training through the flexible curriculum recently endorsed by the ABS as well as the feasibility of establishing advanced GI Surgical Fellowships or other ways to provide training in advanced GI surgery

TASKS

a. Create detailed curriculum for advanced GI fellowship

b. Identify criteria to select sites that could sponsor an advanced GI fellowship
c. Work with FC and ABS—prepare for future (death of MIS fellowship or tracking)

3. Research Working Group
Research
GOAL: To foster the development of new knowledge and techniques that will improve the understanding and treatment of Digestive Disease
TASKS

a. Select recipient of Career Development Award
b. Run resident research seminar
c. Monitor progress of funded research awards
d. Identify ways to leverage SSAT funding for research
e. Work to find SSAT members who can be on NIH Study Sections

Health Care Quality and Outcomes
GOAL: To use the best available knowledge to define meaningful standards and oversee their dissemination in the public domain
TASKS

a. Develop and update Guidelines for treatment of digestive disease
b. Define Quality metrics for treatment of digestive disease
c. Work with other DDW societies to derive consensus and create consensus conferences and publications
d. Identify members who belong to multiple societies (ASCRS, SSO, SAGES, etc.) and offer membership to reps of other DDW societies (AGA, ASGE, AASLD)
e. Contribute ideas and content for a Quality and Outcomes session as part of the annual program

4. Member Services/Policy Working Group
Member Services
GOAL: To serve as the premier member resource center for Digestive Diseases
TASKS

a. Conduct a comprehensive member needs assessment to drive SSAT programs and services

- Identify names of consultants who could advise the SSAT, help establish protocols, coordinate question development and mailings/emails, tabulate/analyze responses, and prepare a report. Request proposals from consultants; interview no more than three consultants and hire one by March 2011.
- Identify a major Task Force comprised of a diverse and representative group of members to participate in the development of the assessment project. Identify a strong Chair of the Task Force who will help drive the agenda and get it done. Appoint the Chair by the end of 2010 and finalize the Task Force by January 2011
- First report to the Board of Trustees on preliminary work and final timeline by February 2011
- Explore various data collection methodologies, including conducting a baseline survey followed by personal interviews by leadership of members who do not participate/attend DDW
- Present survey results to Board of Trustees by May 2011
- Create/build/strengthen new services in part based on needs assessment
- Inform other committees such as Education and program committees on needs

b. Explore the opportunities for SSAT at the "DDW Oasis"

- With the Program Committee, work with DDW-Administration to identify new interdisciplinary programs and communication opportunities that the SSAT could offer within the Oasis—and whether those opportunities are something on which the SSAT could take the lead
- Prepare an outline of ideas and a white paper detailing the pros and cons of—and a budget for—any SSAT offerings

c. Recruitment of new members

- Explore options such as Women's needs, Military needs, etc. for subgroups

d. Set dues policies/member retention
e. Develop mentoring program for young surgeons
Communications Committee
GOAL: To connect the membership to the activities of the society, providing accurate useful information in real time
TASKS

a. Update the Webpage making it a major unifying educational resource not only for our members but for all professional and lay people interested in the current art and science of GI surgical practice

- Write RFP for Webpage update
- Develop Facebook page
- Provide Twitter feed during DDW

b. Oversee the Journal (takes over publications committee)
c. Manage enduring Materials

Public Policy & Advocacy

GOAL: To advocate for patients and Society members to advance treatment of Digestive Diseases, and to nurture the development of SSAT members with expertise in the legislative and political arena

TASKS

a. Advocacy within "the house of medicine"
b. Work with ACSPAC and other Surgical Societies in areas of common interest
c. Coordinate/Be informed by work of the HCQ&O committee

International Relations Committee

GOAL: To help the SSAT interface with societies and members outside the USA and Canada

TASKS

a. Outreach to surgeons and surgical societies outside of the USA and Canada
b. Advise Member Services Committee on benefits structure for international members
c. Develop and asses opportunities to hold joint conferences in other countries
d. Develop and assess medical mission/service opportunities

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Introduction: SSAT/AGA/ASGE State-of-the-Art Conference: Necrotizing Pancreatitis: Novel Minimally Invasive Strategies

C. Max Schmidt

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Abstract
Background Necrotizing pancreatitis is the most severe end of the spectrum of acute pancreatitis. Interventional treatment (i.e., "who, when, and how") of necrotizing pancreatitis is an ongoing source of considerable controversy. Novel minimally invasive strategies are being increasingly employed to perform pancreatic necrosectomy.
Methods The Society for Surgery of the Alimentary Tract, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy recently convened a State-of-the-Art Conference to analyze the experience and evidence that these minimally invasive treatments are beneficial in select patients with necrotizing pancreatitis.
Conclusions This article serves as a general introduction to the State-of-the-Art Conference, Necrotizing Pancreatitis: Novel Minimally Invasive Strategies.

Keywords Necrotizing pancreatitis · Acute pancreatitis · Pancreatic necrosectomy · Laparotomy · Minimally invasive · Retroperitoneoscopy · Laparoscopy · Endoscopy · Interventional radiology · VATS

Introduction

Problem Acute pancreatitis is common and occurs in approximately 200,000 individuals per year in the USA. Necrotizing pancreatitis is on the most severe end of the spectrum of acute pancreatitis and is relatively uncommon. Mortality from necrotizing pancreatitis is significant.

Etiology and Presentation The most common causes of necrotizing pancreatitis in this country are gallstones and alcoholism. A significant number of cases of necrotizing pancreatitis, however, are idiopathic and may be secondary to iatrogenic causes (e.g., endoscopic retrograde pancreatography surgery or trauma), hypertryglyceridemia, drugs, and intraductal tumors (e.g., intraductal papillary mucinous neoplasms). There is a wide spectrum of clinical presentations of necrotizing pancreatitis. Some patients may only have mild abdominal pain or rarely even be asymptomatic. This is exceptional, however, as most presentations are more severe and not uncommonly will include some component of multisystem organ dysfunction or failure.

Evolution of Intervention A significant number of patients with necrotizing pancreatitis will require intervention. Optimal treatment of necrotizing pancreatitis is an ongoing source of considerable controversy. In the past, necrotizing pancreatitis was considered a primary surgical condition requiring surgical intervention. Open pancreatic necrosectomy typically was performed for patients with pancreatic necrosis, while radiologic and endoscopic interventions rarely played even secondary or supportive roles in treatment. Treatment of pancreatic necrosis in the last decade, however, has evolved to include laparoscopic/retroperitoneoscopic, radiologic, and endoscopic interventions as primary treatments of pancreatic necrosis in some institutions. There are few level 1 data on the treatment of

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acute necrotizing pancreatitis.[1] Data are based primarily on retrospective case series of patients with necrotizing pancreatitis. Since novel minimally invasive strategies are being increasingly employed to perform necrosectomy, we convened this SSAT/AGA/ASGE State-of-the-Art Conference to analyze the experience and evidence that these treatments are beneficial in select patients with necrotizing pancreatitis.

Aims The aims of the 2010 SSAT/AGA/ASGE State-of-the-Art Conference, Necrotizing Pancreatitis: Novel Minimally Invasive Strategies are to: (1) understand the presentation spectrum of necrotizing pancreatitis, (2) understand the appropriate management of patients with necrotizing pancreatitis based upon patient presentation and course, (3) understand novel minimally invasive approaches to surgical intervention in patients with necrotizing pancreatitis, (4) understand appropriate patient selection for particular interventions in patients with necrotizing pancreatitis based upon patient presentation and course, and (5) appreciate situations where appropriate management or intervention may be unclear based upon lack of data in the medical literature.

Summary of Papers In the first article, Open Pancreatic Necrosectomy: Indications in the Minimally Invasive Era, Dr. Carlos Fernandez-del-Castillo from Mass General Hospital (Boston, MA) reviews the current indications for open pancreatic necrosectomy. Indications for open necrosectomy historically included only patients with proven infected pancreatic necrosis. It is now clear, however, that patients with sterile necrosis who fail to thrive may also benefit from open necrosectomy. In either case, early necrosectomy is associated with increased morbidity and mortality, and thus, delayed necrosectomy is the preferred approach in managing these patients.[2] Outcomes have improved over time with open necrosectomy. Controlled studies comparing open necrosectomy with minimally invasive alternatives are lacking. Minimally invasive alternatives have been largely employed in highly selected patients in specialized centers, so any uncontrolled comparison to open necrosectomy is bound to be confounded by selection bias. The treatment of patients with necrotizing pancreatitis remains primarily surgical and should be performed by a multidisciplinary team at experienced centers.

In the second article, History, Goals and Technique of Laparoscopic Pancreatic Necrosectomy, Drs. Matthews, Alverdy, and coauthors from University of Chicago (Chicago, IL) review the evolution of laparoscopy in the management of pancreatic necrosis. The International Acute Pancreatitis Guidelines (2002) espoused that pancreatic necrosectomy should aim to remove all necrosis and infected necrosis.[3] It has become apparent, however, that this may not always be necessary or optimal, and a "step-up" approach to intervention may have advantages in select patients. Because percutaneous drainage has achieved complete resolution of infected pancreatic necrosis in select patients, an initial percutaneous approach is a logical first "step" in infected pancreatic necrosis. If necessary, a second step is minimally invasive intracavitary pancreatic necrosectomy along an established percutaneous drain tract. This achieves a port of entry which can be accessed repeatedly to debride necrotic tissue as it becomes amenable to removal according to the patients' response/needs during their recovery. The technique of minimally

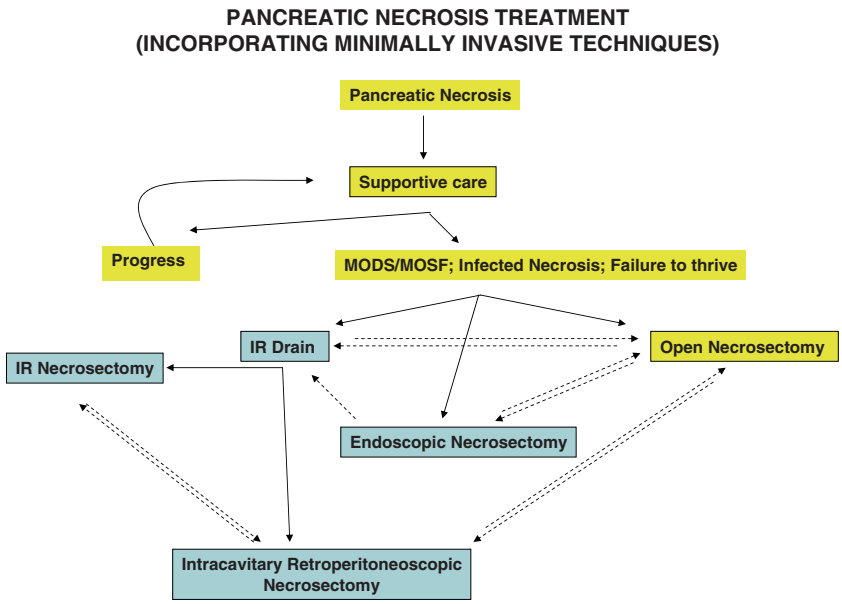

Fig. 1 Progressive treatment algorithm for pancreatic necrosis. The gold standard is shown in yellow and novel minimally invasive approaches are shown in teal. Each of the boxes outlined in black can be endpoints in and of themselves in treatment. Commonly, there is a significant interplay between modalities

invasive intracavitary pancreatic necrosectomy is described extensively and compared/contrasted with traditional laparoscopy with pneumoperitoneum.

In the third article, Endoscopic Pancreatic Necrosectomy, Dr. Evan Fogel from Indiana University (Indianapolis, IN) reviews the endoscopic management of pancreatic necrosis. Techniques of endoscopic necrosectomy are in some respects an extension of endoscopic pseudocyst drainage. Transmural puncture and balloon dilation of cystostomy are common to both. Evacuation of solid material is what distinguishes necrosectomy technically from pseudocyst drainage. This is accomplished by transmural placement of the endoscope through the dilated cystostomy. Evacuation of necrosis is then accomplished endoscopically with the help of lavage, cautery, and various instruments to facilitate debridement. The literature contains mostly small, single-institution, retrospective studies on endoscopic necrosectomy. The largest study to date (Seifert et al.) involved 93 patients at six German institutions and reported 80% initial success, 26% major morbidity, and 7.5% mortality.[4] Current controversies in technique of endoscopic necrosectomy include the use/non-use of EUS to guide initial transmural puncture, necessity of lavage via nasocystic catheter, air vs. carbon dioxide insufflation, balloon size, and whether to accomplish debridement in single vs. multiple sessions. Patient selection remains critical as well as performing endoscopic debridement in centers where surgery and interventional radiology support can assist in the management of bleeding, infection, fistula, obstruction, and other complications of pancreatitis and endoscopic management of pancreatic necrosis.

In the fourth article, Necrotizing Pancreatitis: Interventional Radiology (IR) Management, Dr. Eric vanSonnenberg from Phoenix, AZ and his coauthor review the interventional radiologic management of pancreatic necrosis. In selected patients, catheter drainage alone or combined with antimicrobials (if infected) may serve as primary treatment for pancreatic necrosis. Alternatively, it may serve as a temporizing measure prior to surgery, access point for intracavitary retroperitoneoscopy, or a mechanism to "clean up" undrained collections after surgical debridement. Pancreatic necrosis may be optimally managed with large bore catheters (20–30 French) and multiple (one for each necrotic fluid collection) catheters due to solid/semi-solid necrotic debris. Percutaneous necrosectomy (using baskets, graspers, etc.) may facilitate the radiologic approach to pancreatic necrosis. Several studies have proven the efficacy of this approach in selected patients with pancreatic necrosis. Historically, studies report a range of 50–100% success rate for selected patients with infected pancreatic necrosis.[5,6] More recently, Mortele reported success rates of approximately 50% for sterile necrosis as well.[7]

In summary, minimally invasive treatments are being increasingly used in the treatment of patients with pancreatic necrosis, but the gold standard remains open necrosectomy. Figure 1 is an attempt to capture this in a progressive treatment algorithm for pancreatic necrosis. The gold standard is shown in yellow, and novel minimally invasive approaches are shown in teal (blue gray). Drains may be placed in IR or endoscopy according to location/extent of necrosis and local expertise. A "step-up" approach to necrosectomy is illustrated when an IR drain is placed and then used as access for IR necrosectomy or intracavitary retroperitoneoscopic necrosectomy. Alternatively, an endoscopic drain is placed and then used as access for endoscopic necrosectomy. Each of the boxes outlined in black can be endpoints in and of themselves in treatment. More commonly, there is a significant interplay between the modalities. As an example, a patient may develop failure to thrive, undergo IR drain as access for IR necrosectomy, but ultimately require intracavitary retroperitoneoscopic necrosectomy. If this fails, then the patient may require open necrosectomy. Finally, IR drains may again be employed to drain areas of necrosis inaccessible or that develop after open necrosectomy.

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Open Pancreatic Necrosectomy: Indications in the Minimally Invasive Era

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Keywords Pancreatitis · Debridement · Necrosectomy

The management of pancreatic and peripancreatic necrosis that result from an attack of severe acute pancreatitis has evolved over more than half a century, and deciding who needs an operation, when to operate, and what type of operation to do have been (and to some extent still are) the matter of controversy. This decision making and management have traditionally been done by surgeons but increasingly in specialized centers are done by a multidisciplinary team that includes gastroenterologists, surgeons, endoscopists, and interventional radiologists.

A conventional teaching is that only patients with proven infected necrosis should be intervened upon.[1] This approach is predicated on the relatively high morbidity and mortality that can result from necrosectomy, and that is felt that can only be justified in the presence of infected necrosis since these patients can rarely survive if the necrotic tissue is not removed. However, we and others have shown that patients with sterile necrosis who have symptoms can also benefit from necrosectomy, allowing patients who have been lingering (often for months) with persistent pain and inability to eat to recover.[2,3] Furthermore, as many as 42% of these patients were proven to have infection in the necrotic tissue removed at the time of surgery, and either had no clinical signs of infection or had had negative fine-needle aspiration (FNA) for infection.[3] In our experience, >20% of patients with a negative FNA were infected, proving that over-reliance on this method to dictate the need for intervention can be misleading, and that a rigid dictum of operating only on proven infected necrosis should be abandoned. While the overall mortality for pancreatic debridement remains high (11.4% in our latest published experience with 167 patients who had an average APACHE II of 9.5), patients who had sterile necrosis tend to have better outcomes: the mortality was 4.4%, reoperation rate was 8.9%, and length of stay was 26 days.[3] Other groups have also espoused the philosophy of not restricting debridement to infected necrosis and report as well lower mortality rates in patients with sterile necrosis.[4,5]

There is less disagreement on the issue of timing of surgery. Plenty of empirical data, as well evidence from a small randomized controlled trial, have shown that *early* debridement is fraught with a higher incidence of complications, often needs multiple reoperations, and thus carries a high mortality.[6] For these reasons, most surgeons prefer to delay intervention until the areas of necrosis are well demarcated and liquefaction has begun. There is no exact timing for this, but it usually means 3 to 4 weeks after inception of pancreatitis. A few years ago, we did an analysis on a cohort of 64 patients and correlated time to surgery (i.e., from inception of pancreatitis to surgical debridement) with an outcome score obtained by assigning points to adverse outcomes (such as death, need for ICU stay, reoperation, development of renal failure, enteric fistulae, etc.). Not unexpectedly, outcome scores were lower with delayed surgery, but this difference stopped being statistically significant after day 21.[6] Several other publications have shown similarly better outcomes with delayed surgery.[4,7,8]

Regarding the technique, the surgeon faces many different approaches, including endoscopic, laparoscopic, and percutaneous debridement, as well as the "old

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fashioned" (but time tested) open surgical debridement followed by either continuous lavage, open packing, planned re-explorations, or, as we prefer at MGH, "closed packing." The argument of the newer minimally invasive approaches is that these patients are sick, and avoiding the laparotomy spares extra surgical stress and decreases long-term morbidity. There are no controlled data comparing these different approaches, and the number of patients reported with the newer approaches is very small relative to open surgical series.

There is no question that open surgical techniques can be associated with high surgical mortality and both early and late substantial morbidities. Several reports from the last decade describe mortality rates in excess of 20%.[8–10] However, many other series describe much better survival rates,[3,4,11] and in fact, a recent analysis obtained from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) for calendar year 2007 showed that 30-day mortality for 161 patients undergoing pancreatic necrosectomy was only 6.8%.[12] Although this needs to be interpreted with some caution, given that 30-day mortality may overestimate outcomes for this clinical problem, it nonetheless creates a standard, and this low mortality will have to be matched by the newer techniques if there is any expectation that they will become fully incorporated as a standard treatment for patients with pancreatic necrosis. Furthermore, this group of NSQIP patients is non-selected, many were very ill, and by any criteria were expected to have higher mortality. This needs to be kept in mind when analyzing series of endoscopic, laparoscopic, or percutaneous necrosectomy, which for the most part have been used on highly selected patients. This same NSQIP study also shows that nearly one third of patients required a reoperation and an overall morbidity of 62%.[12] These are certainly outcomes that we hope can be improved upon either by refining open surgical techniques or with minimally invasive ones.

Clinical trials that attempt to address whether lesser invasive techniques are comparable or superior to open operations will be hampered by the reality that patients with necrotizing pancreatitis comprise a very heterogeneous group. This heterogeneity is a hallmark of this disease and comprises not only variability in the patient response to pancreatitis, with some having no dysfunction whatsoever and others having multiorgan failure with the same amount of pancreatic injury, but also very large differences in the extent of pancreatic and peripancreatic necrosis. For example, a patient with necrosis limited to the body of the pancreas and surrounding fat may be a good candidate for endoscopic transgastric debridement, whereas a patient with necrosis extending into the right and left paracolic gutters would not. Other elements that will have to be factored in these trials include the timing of the intervention and the presence or absence of infection.

The lessons learned regarding indications for and timing of open surgical intervention in pancreatic necrosis for sure are being extrapolated to the newer, minimally invasive techniques. The question of whether or not a surgeon should abandon open necrosectomy in favor of something new is a difficult one. Certainly, the temptation to do less in these sick patients (or to transfer their care to another specialist like the endoscopist) can be there, but the risk of serious harm by an inexperienced operator is also quite substantial. In my opinion, the care of these patients needs to continue to be in the hands of a surgeon, and not of an endoscopist or an interventional radiologist. Multidisciplinary management is certainly in the best interest of patients with acute pancreatitis, and identification of suitable cases for primary endoscopic, percutaneous, or laparoscopic debridement will eventually happen if the team is open to innovation. However, it is unlikely that in centers with a successful track record in surgical pancreatic necrosectomy this will be relegated to a secondary role (such as salvage procedures) until overall outcomes are proven to be equal or better. This is the case at the Massachusetts General Hospital, where less than 10% of pancreatic necrosis is managed by endoscopy and none (primarily) by interventional radiology.

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History, Goals, and Technique of Laparoscopic Pancreatic Necrosectomy

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Abstract The surgical treatment of severe acute pancreatitis has significantly changed in the last several years with the advent of enhanced imaging techniques and minimally invasive surgery. Criteria for surgical intervention have been influenced by the use of step-up approaches that provide incremental multimodality interventions with repeat imaging. Here, we provide a brief introduction to the history, goals, indications, and technique of laparoscopic pancreatic necrosectomy. The technique requires a fundamental understanding of the natural history of pancreatitis and its complication. Laparoscopic approaches can be useful as primary and adjunctive therapy for the treatment of infected pancreatitic necrosis.

Keywords Pancreatitis · Necrosectomy · Laparoscopy

Goal of Laparoscopic Pancreatic Necrosectomy

The dogma surrounding the surgical treatment of acute pancreatitis has undergone significant revision as experience and knowledge have emerged to suggest that delaying and performing less surgery, even in cases where disease is severe, is considered to be safe and often effective.[1] The current standard of care in treating acute pancreatitis has been outlined by the International Acute Pancreatitis (IAP) guidelines[2] where conservative management of sterile necrosis is recommended, whereas in cases of infected necrosis, debridement or drainage is advised. Highly experienced centers no longer necessarily adopt the dictum that it is necessary "to remove all areas of necrotic tissue including necrotic pancreatic tissue and any infected necrotic tissue."[2] While it may be necessary to do so in certain cases, it is becoming increasingly clear that an expectant "step-up" approach to debridement and drainage may be a more appropriate strategy to reduce inflammation and eliminate microbial burden. With improvements in imaging, repeated percutaneous drainage with advancing size catheters, and increasing confidence that expectant observation may improve long-term outcome compared to more aggressive open surgical debridement, approaches to more completely debride pancreatic and peripancreatic tissue via smaller incisions have emerged. The minimally invasive approach to debridement offers the benefit of maintaining the compartmentalization of the infection focus while reducing microbial burden without contaminating virgin tissue planes and the larger peritoneal cavity. Avoidance of full abdominal exploration may reduce fistulas, bleeding, and wound complications that are associated with open explorations and commonly required multiple re-explorations. The goals of laparoscopic intracavitary pancreatic necrosectomy are to evacuate as much necrotic and infected tissue in a safe manner while creating a minimal access portal of entry into the necroma that can be maintained for as long as needed to perform repeat debridements. This approach departs from the surgical instinct to completely debride all infected tissue with a single operative intervention and offers the benefit of less bleeding and systemic inflammation with the opportunity to re-image and rethink the surgical strategy.

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Image-Guided Catheter Drainage: The First Step

Although initially met with skepticism, percutaneous drainage of infected pancreatic necrosis has been achieved in selected cases with complete resolution of infection. While it seems counterintuitive that large particulate matter can be effectively controlled and evacuated by percutaneous drainage alone, in some patients the enzymatic breakdown of the necroma produces liquefied contents which can be successfully evacuated through the catheter. This process is aided by the appropriate antibiotic selection and penetration into the infected tissue. As early as 1984, attempts at image-guided catheter-based drainage were reported.[3] In 1998, Freeny et al. published a series of patients with infected necrosis treated by computed tomography (CT) guided drainage.[4] In their series of 34 patients, 26 out of 34 (76%) patients had clinical improvement with catheter drainage, and 16 out of 34 (47%) had complete cure measured by resolution of necrotic collection with catheter drainage alone. This series notes the frequent requirements for catheter upsizing or exchange (four per patient) and frequent irrigation required in order to maintain catheter patency in the face of the thick contents of the necroma. Steiner et al. published a similar series the same year of 25 patients treated with CT-guided drainage of pancreatic necrosis.[5] Of the 18 patients treated primarily by interventional radiology (IR) drainage, 14 (77%) experienced clinical improvement with catheter drainage and eight (44%) were "cured" by drainage alone. Based on these and other reports, it seems logical that the first step in the expectant treatment of infected pancreatic necrosis is to obtain adequate percutaneous image-guided drainage of major sites of visible necroma formation, to culture all draining material and to follow the clinical course of the patient to assess the need for catheter upsizing or surgical debridement. With experience, the timing of early laparoscopic debridement will be balanced against repeated percutaneous drainage, upsizing, and imaging. The timing of each approach must be individualized to the clinical course of the patient and the experience of the managing surgeon. As the technique and instrumentation develop around laparoscopic necrosectomy, it is anticipated that early definitive minimally invasive debridement will reduce the need for repeat imaging and shortened length of stay.

History of Direct Visualization Minimally Invasive Pancreatic Necrosectomy

There have been essentially three techniques of direct visualization minimally invasive pancreatic necrosectomy described over the last 10 years. The first technique involves making a posterior incision to enter the retroperitoneum and directly visualize the space with a nephroscope or similar type instrument. Single or multiple access site incisions can be used and repeated drainage achieved. Second, "traditional" (intraperitoneal) laparoscopy has also been described whereby pneumoperitoneum is established and the retroperitoneum is entered, usually via an opening in the transverse mesocolon or gastrocolic ligament. With direct opening of the necroma, several ports are used to debride, irrigate, and lavage the abdominal cavity. The final and third approach, which is our preferred approach, is to percutaneously enter the necroma cavity extraperitoneally and evacuate fluid and tissue using conventional laparoscopic equipment. We term this approach laparoscopic intracavitary pancreatic necrosectomy (Lap-ICPN).

In 2000 Zhu et al. published a series of ten patients with severe acute pancreatitis that underwent "traditional" laparoscopy (with pneumoperitoneum) and debridement of necrotic pancreas.[6] After lavage with sterile saline, large bore catheters were placed, and postoperative lavage was continued for 7 to 14 days. While this was the first description of "conventional" intraperitoneal laparoscopy for pancreatic debridement, it must be noted that these patients were operated within days of presentation of severe acute pancreatitis. Parekh reported in 2006 on a series of 18 patients[7] that underwent similar "conventional" laparoscopic debridement using a "hand assist" port. Two patients (11%) died, two (11%) required subsequent "open" debridement, and two (11%) required repeat laparoscopic intervention.

Intracavitary Debridement

In 2000, our group reported the first description of the intracavitary approach to necroma debridement using conventional laparoscopic equipment.[8] Immediately following this report, Carter, McCray, and Imrie described a series of ten patients using a similar technique of image-guided catheter placement and dilation of the tract to establish a direct access to the necrotic cavity.[9] This latter group used nephroscopic and endoscopic instruments to perform irrigation and debridement and the use of postoperative continuous lavage instead of closed drains. In 2001, Horvath et al. described the results for six patients using a similar technique, this time with two ports to allow for irrigation and debridement under direct visualization.[10] Again, image-guided catheters were used to temporize patients via drainage of collections; if further debridement was deemed necessary, patients were taken to the operating room where two 10-mm trocars were placed via a flank incision using the image-guided catheters as guides. More recently, Bucher et al. described a single port technique in eight patients.[11] A single 12-mm trocar was placed over a previously placed drain (either postsurgical or image The

Society for Surgery of the Alimentary Tractguided) and using a single 12-mm port, 5-mm instruments were used under direct visualization with a 5-mm laparoscope via the same port. A jet lavage/irrigation was again used along with blunt graspers to remove as much solid necrotic tissue as was deemed safe. On completion, a two channel drain was used for continuous postoperative lavage.

Although many excellent reviews of the various series of minimally invasive pancreatic necrosectomy have been recently published, comparative trials are still lacking.[12,13] Table 1 lists the complication rates, requirement for open laparotomy (or re-laparotomy), and mortality rates for selected studies of both minimally invasive and traditional open techniques.

Terminology

A brief note on terms and definitions is warranted. These techniques have been referred to as laparoscopic, nephroscopic, endoscopic, or visually assisted retroperitoneal debridements.[12,14] We prefer the term "minimally invasive intracavitary pancreatic necrosectomy" because it emphasizes the benefits these techniques offer. "Minimally invasive" techniques offer smaller incisions, less pain, more rapid healing, and most importantly potentially incite less of an inflammatory and catabolic response than a large open incision. "Intracavitary pancreatic necrosectomy" emphasizes the fact that this technique allows direct access to the necroma cavity with minimal disruption of normal tissue planes or seeding of healthy tissue with infected, necrotic debris.

Technique of Intracavitary Pancreatic Necrosectomy

The steps and goal of Lap-ICPN, in accordance with the IAP guidelines,[2] are to access the pancreatic necroma cavity safely and evacuate as much material as possible. The goal should be to perform this safely with the expectation that repeat imaging along with repeated assessment of the clinical course will dictate the need for additional debridement. In many cases, multiple cavities connect via small channel loculations. This becomes apparent with subsequent debridements where the irrigation of one cavity results in necroma effluent exiting a seemingly remote cavity. As the necroma liquefies and the channels connecting the retroperitoneal cavities become unobstructed, irrigation can proceed once large bore (i.e., 32-French) drainage tubes have been placed into the various cavity sites. Despite the concern for lavage or insufflation-induced translocation of bacteria from infected necrosis into the systemic circulation, we have not witnessed an exacerbation of the septic response in any of the cases we have performed to date. This may be because of patient selection which invariably involves patients in the late course (3–6 weeks) of pancreatitis when the acute inflammatory response is quiescent and the necromas have demarcated and compartmentalized. However, before proceeding with Lap-ICPN, it is important to verify that antibiotic schedules are fully accounted for and that adequate antibiotic prophylaxis is present at the time of surgery. As the pancreatic necromas are most often deep below the anterior abdominal wall surface, percutaneous, image-guided access is achieved via a flank approach with catheter placement. It is often the case that lateral flank drains on the opposite site of the abdomen are present. To complete a dual cavity procedure, positioning may require very wide draping. Alternatively, one can complete the first side and re-drape for the second. In most cases, Lap-ICPN is performed 1–3 weeks following image-guided percutaneous drainage. With already well-demarcated and compartmentalized cavities at the time of clinical presentation, we have performed the procedure as soon as 2 days following IR drainage.

Accessing the Cavity The drains used by IR are often the pigtail variety that are fenestrated and open ended with a

Table 1 Major complications are defined according to the original reference and have not been standardized

Technique	Reference	Number	Major complications	Laparotomy required	Mortality
Image-guided catheter placement	4,5	42	NR	28 (67%)	1 (2%)
Retroperitoneal necrosectomy	12	141	58 (41%)	18 (13%)	22 (16%)
Endoscopic necrosectomy	12	157	31 (20%)	NR	7 (5%)
Laparoscopic necrosectomy	12	46	NR	5 (11%)	3 (7%)
Open debridement with closed drainage	14	167	NR	25 (15%)	19 (11%)
Pooled NSQIP data	15	161	62%	NR	6.8%

Babu and Siriwardena[12] include any technique that uses a laparoscope as "laparoscopic necrosectomy," and the data included in this table from their review pools both "traditional" laparoscopy with pneumoperitoneum[6,7] and "laparoscopic intracavitary pancreatic debridement,"[8,10,11] which we discuss as separate techniques.

NR Not recorded

nylon looped configuration to maintain the pigtail curl, thus preventing dislodgment. These drains can be easily accessed using the appropriate gauge guidewire. Depending on the level of experience and expertise, guidewire access to the necroma cavity can be obtained with or without fluoroscopic guidance. We prefer to use a special guidewire whose end is flexible and soft for at least 40–60 cm allowing it to curl repeatedly within the cavity. Under fluoroscopic visualization, this allows the operator to gain a sense of the size of the cavity to be entered. The wire should be reasonably inflexible below the curled end as the multiple layers of the abdominal wall can be difficult to traverse with the laparoscopic trocar. Often, the percutaneous IR-placed drains are very close to the rib cage, which can present a challenge. Once the wire is securely positioned, a laparoscopic trocar is placed over the wire using fluoroscopic guidance, being careful to avoid angulation of the wire and a smooth transition of the trocar into the cavity. A skin incision is used to extend the wire entry site and we begin with a 5-mm smooth trocar. Once we verify that the trocar is within the cavity, we next gently admit the 5-mm laparoscopic irrigation/suction device into the cavity to remove the liquid debris. We next verify that we are within the cavity by using a 5-mm 0° laparoscope and gentle insufflation. Once proper location in the necroma is established, we then place a laparoscopic kitner into the cavity via the 5-mm trocar to use as a stylette for removal of the 5-mm trocar and placement of the 15-mm trocar. This is completed under fluoroscopic control if needed. Once the cavity is accessed, we then again verify that we are within the cavity by performing a laparoscopy with insufflation. Once the cavity is entered with the 15-mm trocar, we essentially use three techniques to clean out the necroma cavity and fully debride all of the tissue (see Fig. 1).

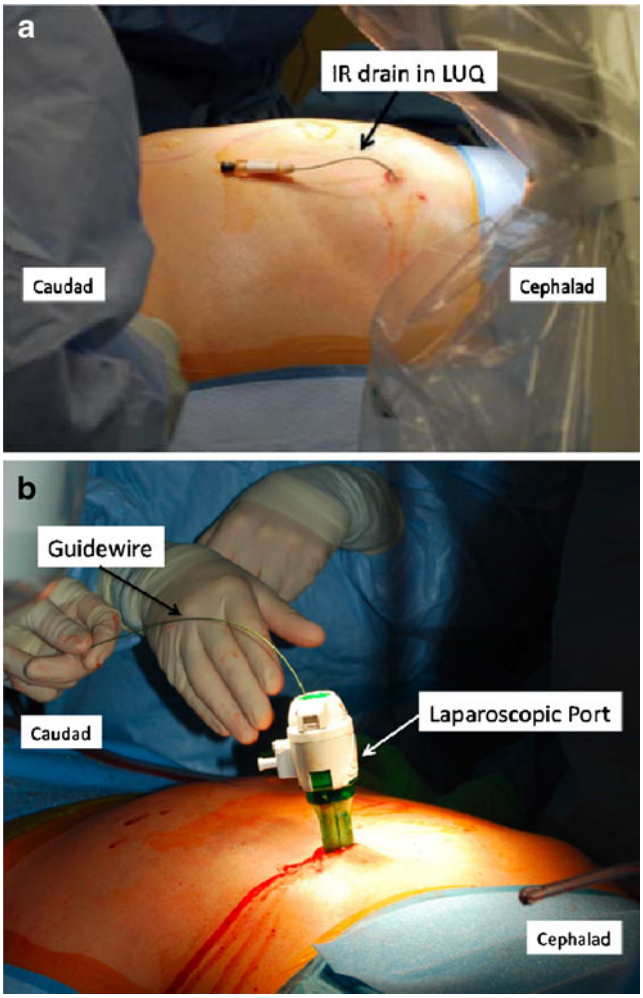

Fig. 1 **a** A patient is prepped and draped with IR drain shown in left upper quadrant (*LUQ*). **b** Using the Seldinger technique, a guidewire was inserted into the necroma through the IR drain. The drain was removed over the guidewire and the laparoscopic port was placed into the necroma over the guidewire

Debridement Maneuver Initially, we do not use insufflation but rather remove the seal on the "cap" of the trocar and using both the 5-mm 0° laparoscope with either the suction/irrigator or a 5-mm grasper, we remove large pieces of necroma under direct visualization at the immediate base of the trocar. The assistant holds the trocar in place and moves it in a circular motion to visualize the greater expanse of the cavity (see Fig. 2).

Inspection Maneuver Periodically, we will reattach the trocar head, insufflate, and inspect the entire cavity. In our opinion, it is best to perform the cavity necroma evacuation with a single 15-mm trocar not two trocars. With insufflation and the seal of the trocar, it is difficult to maintain pressure while inserting two 5-mm instruments through the valve. For this reason, we often just inspect during insufflation, maintain the position of the trocar at the site of heavy contamination and tissue accumulation, and remove the trocar head and continue using the debridement maneuver with multiple instruments operating co-axially using the 5-mm scope for direct visualization.

Irrigation Maneuver Once we feel we have completed the debridement, we will use a jet lavage instrument inserted into the cavity and then we will irrigate the cavity with a high volume of saline. The trocar head is again off; the trocar can be placed at an angle which will allow the overflow effluent to pour into a receptacle by gravity and then jet lavage/gravity irrigation procedure is repeated while periodically using the "inspection maneuver" to monitor progress and direct further debridement or lavage.

It is often the case that pulsations in the projection of major arteries can be visualized during the procedure. If tissues are adherent to pulsatile structures, we avoid

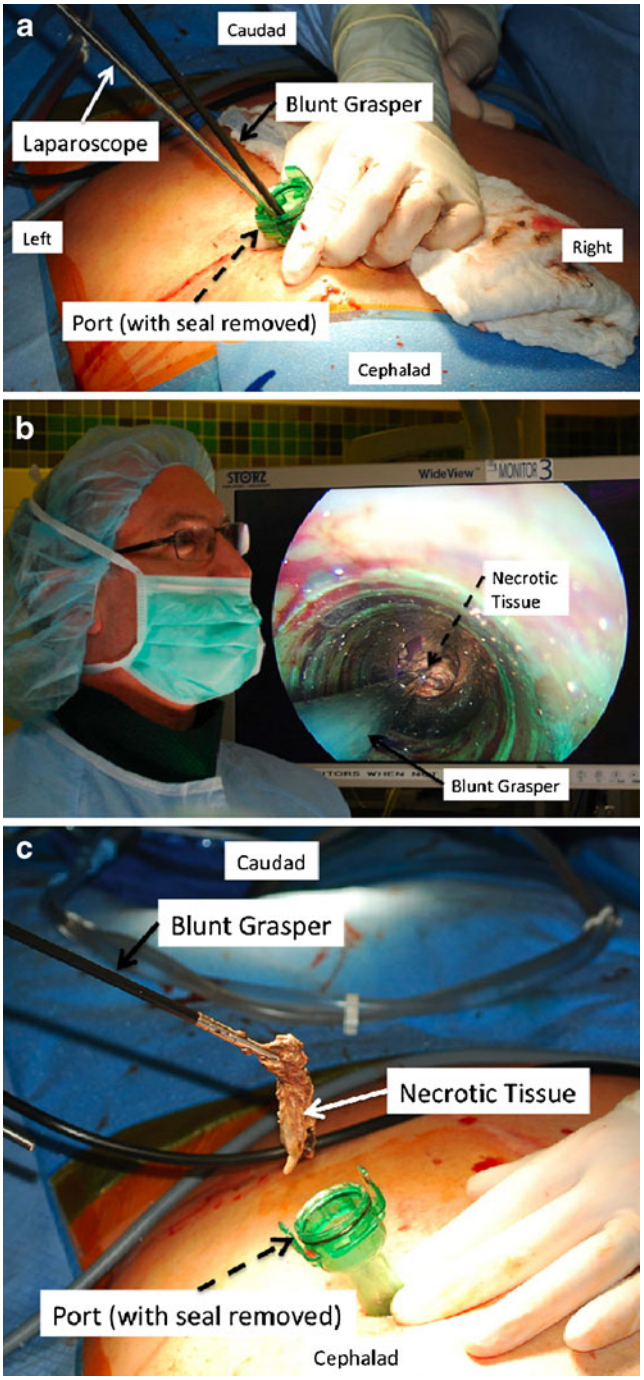

Fig. 2 **a** Debridement technique: the white seal on top of the port (*dashed black arrow*) has been removed and the 5-mm blunt grapser (*solid black arrow*) is being used to debride necrotic tissue under direct visualization with the 5-mm 0° laparoscope (*white arrow.*). **b** Debridement technique: the view of the contents of the necroma, without insufflation, from the laparoscope is shown. The blunt grasper (*solid black arrow*) is seen manipulating the necrotic tissue (*dashed black arrow*) at the base of the laparoscopic port. **c** Debridement technique: removing necrotic tissue (*white arrow*) using the blunt grasper (*black arrow*)

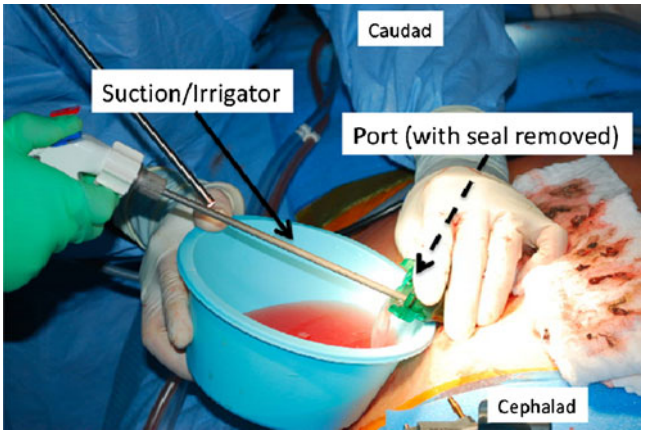

Fig. 3 Irrigation technique: the suction irrigator (*solid black arrow*) is used to irrigate the contents of the necroma

unnecessary debridement. In this case, a direct high-pressure irrigation often suffices (see Fig. 3).

Extent of Debridement Keep in mind that at the termination of the procedure with placement of a large bore drainage tube (i.e., a 32-French red rubber catheter), repeat Lap-ICPN becomes relatively simple as a large tract is already established, and trocar access is easily facilitated. Repeated inspections under insufflation often demonstrate significant necrotic debris seemingly originating from a distant corner of the necroma cavity. This recess may actually be a channel leading to another necroma cavity. It is important to recognize that Lap-ICPN can be considered a staged procedure that in our experience, carries very little morbidity in terms of provoking an inflammatory response. Hemorrhage can occur during the procedure, and the operating team should always be prepared for rapid conversion. For these reasons, we tend to complete as much of a necrosectomy as is well tolerated and safe and plan for repeat exploration(s) as needed. Part of this success and low morbidity may be the timing of the procedure, temporizing with image-guided catheter placement, recognition that complete debridement may not be necessary, and the technique itself. Once the cavity has been irrigated and full cavity inspection during insufflation laparoscopy has been deemed adequate, we place a 32-French fenestrated red rubber tube into the cavity and use a 2-0 nylon to affix it to the skin. The second cavity (if present) can then be similarly approached. As we have mentioned previously, when clearing out the second cavity and performing high-volume irrigation, it is often the case that the two cavities have been discovered to communicate by effluent draining from one site to the other. In some cases, it is possible to flush the cavity out. Repeat imaging and repeated Lap-ICPN can often establish the degree of completeness of the necrosectomy and the anatomy of the necroma cavities.

Summary

Although direct prospective studies lag behind the ongoing developments in this technique, we anticipate they will be forthcoming as experience with this technique becomes more widespread. It is interesting to note that four separate groups, almost simultaneously, developed minimally invasive techniques to achieve direct access to the necrotic cavity using image-guided catheters as both a temporizing method as well as assisting in obtaining surgical access; these same studies emphasized the use of laparoscopic and pulse irrigation devices as effective means of debridement.[9–12] These studies utilizing image-guided drainage as a temporizing measure provide further support for the "step-up" approach to managing pancreatic necrosis that is currently being evaluated in the PANTER trial.[14] This ongoing multi-institution trial prospectively randomizes patients with pancreatic necrosis who fail conservative management to either:

1. "Step-up" approach to pancreatic necrosis, as defined by a progression from catheter drainage to video-assisted retroperitoneal debridement to open debridement if required.
2. Maximal open debridement as the initial intervention after failing conservative therapy.

This trial will allow a direct comparison of open debridement to "grouped" minimally invasive therapy at the discretion of the surgeon.

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Endoscopic Pancreatic Necrosectomy

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Abstract Traditionally, patients with symptomatic sterile pancreatic necrosis or infected necrosis have been managed by open surgical debridement and removal of necrotic tissue. Within the last decade, however, reports of endoscopic pancreatic necrosectomy, an alternative minimally invasive approach, have demonstrated high success rates and low mortality rates. This report describes the indications, technique, and study outcome data of the procedure. While our experience with this technique has recently increased, better selection criteria are needed to identify patients who are most suitable for endoscopic therapy.

Keywords Pancreatic necrosis · Endoscopic necrosectomy

Acute necrotizing pancreatitis, defined as local or diffuse areas of nonviable pancreatic parenchyma, occurs in 15–20% of cases of acute pancreatitis. If the necrosis remains sterile, patients may have significant morbidity, but usually respond to aggressive but conservative supportive care. Mortality is approximately 10%. Intervention consisting of debridement or drainage of fluid collections may be indicated in sterile necrosis if patients have persistent narcotic-requiring pain, inability to eat, gastric outlet or biliary obstruction, or failure to thrive—so-called symptomatic necrosis.[1] Alternatively, infected necrosis may develop in 40–70% of cases[2] and frequently is responsible for late clinical deterioration of organ function. Despite advances in critical care over the last few decades, infected necrosis remains the major life-threatening complication of acute pancreatitis, with mortality rates reaching 30%. Traditionally, drainage of necrotic material in patients with symptomatic sterile necrosis or infected necrosis has been accomplished surgically via laparotomy. However, a recent meta-analysis[3] reported the median mortality rate of open surgical approaches to be 25% (range, 12–56%). Minimal invasive approaches with high success rates and lower mortality rates are therefore of interest.

Endoscopic drainage of chronic pancreatic pseudocysts is a well-established safe and effective procedure when performed in expert centers. This technique involves a transmural (transgastric or transduodenal) puncture of the cyst wall, followed by balloon dilation of the cystostomy and subsequent placement of double-pigtail stents into the cavity, allowing for drainage of cyst contents into the gastrointestinal tract. Endoscopic ultrasound may facilitate the initial puncture of the cyst, particularly in cases where a bulge is not clearly visible endoscopically. Transpapillary stents may also be placed across the site of duct disruption in communicating pseudocysts, if feasible. Effective drainage can usually be accomplished with stents alone since pseudocyst contents are usually liquid. If internal debris is present, a nasocystic irrigation catheter may also be required. On the other hand, any intervention for necrosis differs from that of pseudocysts because of the need to evacuate solid material.[4] Failure to do so may lead to infection of the cavity with systemic spread. Baron et al.[5] initially reported endoscopic drainage of organized pancreatic necrosis, previously considered sacrilege.[6,7] Eleven patients (eight sterile, three infected) underwent endoscopic drainage, ten with two 10-F double-pigtail stents placed into the cavity. After two patients treated by transgastric drainage alone developed infectious complications, eight subsequent patients had concurrent placement of a 7-F nasobiliary drain into the cavity, with lavage of the

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collection through this drain for a mean of 19 days (range, 10–30). It was suggested that this lavage might help liquefy the necrotic material. Complete drainage was achieved endoscopically in nine out of ten patients in whom the collection was entered. The mean number of endoscopic procedures required for resolution was 2.7, and five patients (45%) developed significant complications (infection in four, bleeding in one). However, 60% of patients who were initially successfully treated developed recurrent collections within 2 years.[8]

Seifert et al.[9] were the first to describe endoscopic ultrasound (EUS)-guided transmural puncture and subsequent drainage of cavities in patients with infected necrosis. In their series of three patients, the fenestration created was dilated with a 16-mm balloon, allowing for passage of a therapeutic gastroscope into the cavity, offering direct visualization of the necrotic material. Endoscopic debridement/necrosectomy was then accomplished using an assortment of endoscopic accessories, electrocautery, and lavage. The authors reported no additional morbidity with this technique, and their patients were well at 6–9 months of follow-up. Subsequently, several investigators have demonstrated that this form of minimally invasive therapy may be effective and reasonably safe,[4,10–16] as illustrated in Table 1.

Papachristou et al.[4] have reported their experience with 53 patients who underwent endoscopic drainage of sterile (27, 51%) and infected (26, 49%) walled-off pancreatic necrosis. In this retrospective series which took place over an 8-year period, the endoscopic debridement technique evolved over time, but generally followed the same principles as pioneered by Seifert et al.[9] Lavage was accomplished via a nasocystic catheter in 70% of patients and via a jejunostomy tube to the necrotic pancreas through a percutaneous endoscopic gastrostomy tube in 19%. With a median of three procedures performed per patient (range, 1–12), successful resolution of necrosis was achieved in 43 of 53 patients (81%). Complications occurred in 11 patients (21%), of which bleeding occurred in nine, all managed non-operatively. This study identified patients with walled-off necrosis as those which might be successfully managed by this minimally invasive endoscopic approach, particularly those with necrosis involving the lesser sac, amenable to transmural drainage.

A multicenter study presented by Seifert et al.[16] is the largest series to date evaluating endoscopic pancreatic necrosectomy, with long-term outcome. This retrospective study included 93 patients with infected necrosis from six German tertiary referral centers. Transmural access to the retroperitoneal cavity was achieved at the initial endoscopic session, followed by stent insertion, with or without irrigation catheter placement. Balloon dilation (15–20 mm) was then carried out at the next session, allowing for gastroscope insertion into the cavity, followed by endoscopic removal of necrotic debris using forceful irrigation, suction, snares, forceps, and stone removal baskets. Repeated sessions were performed at intervals of 1–4 days until all necrotic material had been removed. Initial clinical success was noted in 80% of patients. Major complications were seen in 26% of cases, with a mortality rate of 7.5% at 30 days. The authors regarded these complication rates as acceptable given the higher rates reported in surgical series. Of those patients successfully treated initially, 84% had sustained clinical improvement after a mean follow-up period of 43 months.

As can be gleaned from Table 1, endoscopic debridement offers an attractive alternative in the management of select patients with necrotizing pancreatitis, with good efficacy and a low mortality rate. However, several issues require further study. Some investigators insist that EUS be used to establish transmural access, allowing for precise puncture localization, even in the absence of intraluminal bulge, as well as avoidance of vascular structures,[17] while

Table 1 Selected series of endoscopic therapy for pancreatic necrosis

Authors (reference)	Patients (*n*)	Infected (%)	Mortality (%)	Success n (%)	Complications
Baron and Morgan[10]	11	27	0	9 (81)	Bleeding, 9%; infection 36%
Charnley et al.[11]	13	85	0	12 (92)	None
Papachristou et al.[4]	53	49	0	43 (81)	11 (21%) bleeding, *n*=9
Voermans et al.[12]	25	100	0	23 (93)	major bleeding, 4%; minor bleeding, 30%
Navaneethan et al.[13]	8	50	12.5	7 (87.5)	perforation of cyst wall, 12.5%
Mathew et al.[14]	6	100	0	5 (83.3)	None
Gardner et al.[15]	25	24	0	22 (88)	Bleeding, 32%
Seifert et al.[16]	93	100	7.5	75 (80) initial, 63 (68) long term	24 (26%): 13 bleeding, 5 perforations, 2 fistulae, 2 air emboli, 2 other organs
Total	234	74	3.4	196 (84)[a]	57 (24%)

[a] Includes initial success rate from Seifert et al.[16]

others have shown that a similar outcome can be achieved with the duodenoscope.[18] Balloon dilation of the transmural tract is safe, with large balloons required to allow for passage of the gastroscope into the cavity. The ideal balloon size has not been established, but a non-randomized series did identify balloon size to be correlated with success of the endoscopic necrosectomy.[15] The therapeutic endoscopist needs to have his full armamentarium of endoscopic accessories available as debridement of solid tissue adherent to the walls of the cavity may be very difficult and time-consuming. Need for a nasocystic irrigating catheter has not been standardized and likely is dependent on the amount of solid tissue remaining at the end of a session. Some investigators have attempted the removal of all necrotic material in a single session, whereas others have advocated repeating the sessions at variable intervals until all the necrosis has been removed.[15,16,19]. Barthet and Ezzedine[17] have suggested that bleeding risk may be less by repeating the sessions more frequently as this complication tends to occur during the removal of the necrotic tissue. Prolonged endoscopic procedures may be complicated by air embolism,[16,17,20] leading to the use of carbon dioxide instead of air in some centers. Despite these unanswered questions, endoscopists may be eager to proceed with this new and exciting technique. However, given the potential for life-threatening complications which may arise, endoscopic necrosectomy should only be undertaken by expert pancreatobiliary endoscopists who are comfortable in the management of these complex, very ill patients. Radiologic and surgical support must be available to treat infectious and bleeding complications not amenable to endoscopic therapy.[7] Most important, however, is the answer to the following question: which patients should be considered for endoscopic necrosectomy? In the absence of prospective trials and cost–benefit analyses, it is difficult to propagate this technique as a replacement for surgery.[1,7] While there may be a role for endoscopy in the management of certain patients with organized pancreatic necrosis, it is clear that many patients will continue to require a multidisciplinary approach by gastroenterologists, pancreatic surgeons, and interventional radiologists.[12]

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Interventional Radiology for Necrotizing Pancreatitis

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Abstract Necrotic pancreatitis is a complex clinical entity that requires collaboration of care from surgeons, gastroenterologists, and interventional radiologists. CT scans play a pivotal role in the diagnosis of pancreatic necrosis, while image-guided percutaneous pancreatic drainage is a safe and effective treatment method in certain cases. The diagnostic criteria for pancreatic necrosis, indications for pancreatic drainage, technique, and efficacy are discussed in this article.

Keywords Pancreatic necrosis · Pancreatitis · Percutaneous catheter drainage · Interventional radiology

Introduction

Acute pancreatitis has a wide spectrum of presentations that ranges from self-limited to life-threatening diseases. The possible complications of acute pancreatitis are many and include fluid collections as a frequent manifestation.[1] These fluid collections also have a wide range of presentations and include the so-called acute peri-pancreatic fluid collections, pseudocysts (sterile or infected), abscesses, and pancreatic necrosis (sterile or infected).[2] The latter category will be the main focus of this manuscript.

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Diagnostic Criteria

Several clinical and radiologic scoring systems exist to diagnose acute pancreatitis.[3–7] Balthazar et al.[5] developed the first widely used CT severity index model that stratified pancreatitis by degree of inflammation and necrosis. Other authors later modified this grading scheme by simplifying it and including an assessment of extrapancreatic complications. These authors stated that the modified CT severity index correlated more closely with patient outcome measures than the previous model.[7] Intravenous contrast administration is essential to diagnose necrotizing pancreatitis using CT criteria. Normal pancreatic parenchyma measures 40–50 Hounsfield units (HU) on unenhanced CT and increases to 80–90 on enhanced CT. If the HUs are below 80, and especially if <50 HU, pancreatic necrosis or another type of collection should be suspected.[8]

Necrotic pancreatic fluid collections can be sterile or infected. The imaging appearance can be identical, however. Occasionally, retroperitoneal or lesser sac gas is detected, suggesting infection, although necrosis without infection may appear as gas on CT also. At times, a dissociation exists between the CT appearance and the patient's status. Obviously, the patient's clinical appearance and discussion with the referring clinician takes precedence over imaging findings in deciding what actions should be undertaken. It is essential for radiologists performing interventional radiology procedures to evaluate patients clinically.

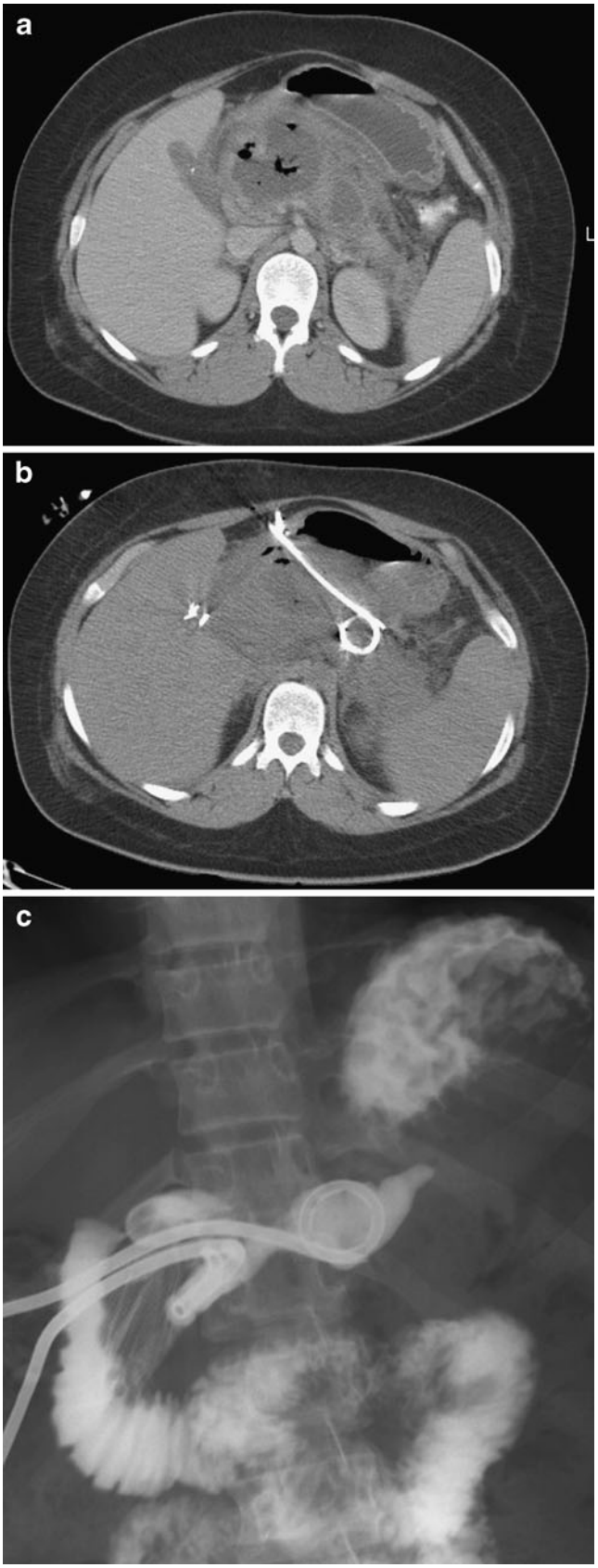

Fig. 1 **a–c** Successful percutaneous drainage of complex pancreatic necrosis from gallstone pancreatitis: **a** Axial CT scan demonstrates multiple necrotic collections with gas (Balthazar grade E). **b** Axial CT scan shows one of three large-bore percutaneous drains into one necrotic collection. **c** Catheter sinogram reveals multiple percutaneous catheters in the now decompressed collections, but with spontaneous communication to the duodenum. After 1 month of drainage of these infected collections, the patient was cured

Indications for Percutaneous Drainage

The decision for percutaneous drainage of necrotic pancreatic fluid collections is based on numerous factors: the patient's clinical status, prior surgery or interventions, sterile vs. infected necrotic fluid collection, degree of liquefaction, and other comorbidities such as multisystem organ failure. Close cooperation and communication between surgeons, gastroenterologists, and interventional radiologists are essential.

Percutaneous drainage alone for sterile necrosis, or combined with antibiotics for infected necrosis, can be curative. Catheter drainage also may be a temporizing measure prior to surgery[9], or, conversely, a follow-up procedure to "clean up" after surgery. The two disciplines and procedures commonly are complementary to manage pancreatic necrosis. Contraindications to percutaneous drainage consist of solid necrosis, active bleeding, uncorrectable coagulopathy, phlegmonous tissue, pseudoaneurysm, and an uncooperative patient.

Technique

US or CT can be used to guide percutaneous drainage. However, CT is utilized far more due to its superior resolution and spatial detail, particularly with respect to surrounding structures that should be avoided (Fig. 1a). The routes for catheter drainage are numerous, but a direct approach is preferred if possible, attempting to avoid bowel or solid organs. The catheter should be positioned so that the largest number of side holes lies in the most dependent part of the fluid collection (Fig. 1b). The number of percutaneous drainage catheters depends on the number of fluid collections; ideally, there should be one catheter for each major necrotic fluid collection. Since pancreatic necrosis often contains both liquefied and solid components, large-bore catheters (20–30 F) may be required.

After the catheter has been placed, daily monitoring of output is routinely performed, as well as frequent irrigation with saline to ensure patency of the catheter and aggressive cleansing of the cavity or cavities. Furthermore, daily Interventional Radiology ward rounds are essential to evaluate the patient's status, the efficacy of the drainage, catheter wound sites, and laboratory parameters. Follow-up imaging can be done to evaluate drainage response (Fig. 1c). If there is a lack of clinical improvement, poor

drainage output, or the presence of persistent fluid collections on imaging, additional catheters or manipulations are done. Commonly, these additional maneuvers will be crucial to the effectiveness of percutaneous drainage. Conversely, inadequate follow-up by radiologists may sabotage a potentially successful outcome.

Lastly, percutaneous necrosectomy can also be performed if large solid pieces of necrotic material impede catheter drainage. Techniques that have been implemented for percutaneous necrosectomy include percutaneous baskets, snares, or forceps to remove debris through large (up to 30 F) tracts,[10–13] similar to what interventional radiologists and urologists use for percutaneous stone management in the kidneys.[14]

Results

Several studies have discussed the effectiveness of percutaneous catheter drainage for pancreatic necrosis.[8,10,11,15–17] In an early study of 34 patients, 47% were cured with percutaneous catheter drainage alone, while sepsis was controlled in 74%.[10] Another study reported a comparable overall success rate (49%) in 35 patients, with similar success rates between percutaneous drainage of sterile (50%) and infected (46%) necrotizing pancreatic collections.[17] In a study of 20 patients, a 100% success rate was reported using large-bore catheters with large side holes coupled with suction catheters, stone baskets, and lavage fluid for debris removal.[11] Catheters can remain for weeks to months, but as patients improve, follow-up can be done on an outpatient basis in Interventional Radiology clinics. Catheter removal occurs when the patient is clinically well and there is no drainage or recurrence of collections.

Spontaneous communication with the gastrointestinal tract occurs infrequently, but serves as another egress route for the pancreatic collection; despite the spontaneous communication, percutaneous drainage typically is successful. Pancreatic collections including necrosis can obstruct the bile ducts, pancreatic duct, or gastrointestinal tract; these types of obstructions can be indications for another interventional radiologic, endoscopic, or surgical procedure. Complications, albeit infrequent, can include bleeding, sepsis, or perforation.

Conclusions

Percutaneous catheter drainage is an effective and safe treatment method for necrotizing pancreatitis. It serves either as curative treatment in itself or complementary to surgery (either before or after an operation). Lastly, careful catheter care and close cooperation among surgeons, gastroenterologists, and interventional radiologists is *sine qua non* to ensure effective treatment of pancreatic necrosis.

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ORIGINAL ARTICLE

The Evolving Surgeon Shortage in the Health Reform Era

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Abstract The evolving surgeon shortage is occurring at a time of societal change. For one of the first times in history, a scientific revolution is occurring while the organization of health care is also changing. With a demand for a more quality health care and a population that has both aged significantly and grown by ten million citizens each decade, the shortage of health care providers is problematic. For surgery, the shortage is particularly challenging. In 1981, 1047 surgeons were certified by the American Board of Surgery; in 2008, that number had dropped to just 909.

Keywords Surgeon shortage · Health care · Change

The twenty-first century will be the first time in history that revolutionary scientific and social changes in medicine occur at the same time. Health care is a public right and a positive good. The quality of health care contributes to the stability and quality of a society. The debate over health care reform has largely ignored a core problem, which is the shortage of health care workers. It is necessary to increase the number of health workers of all types, and also to define priorities of focus to enhance the number of some critical shortage specialties, such as general surgeons.

It is frequently stated that the health care system of the United States is "broken." However, Carl Becker, Nobel Laureate in Economics at the University of Chicago, wrote that the greatest gift of the twentieth century was longer life.[1] He noted the increase in life expectancy from 45 years in 1900 to 80 years in 2000. Our expensive system is producing results with regard to longevity and quality of life.[2]

Considerable analysis, proposed solutions, and multiple political promises have emerged as discussions on the reform of our health care system. It was one of the leading domestic issues of the lengthy presidential campaign. All candidates for the presidency have discussed plans for health care reform, focusing primarily on access and cost. Neither candidate addressed the crisis looming because of the disconnect between the fast-growing shortage of health care workers and the expanded coverage implicit in their current health care proposals.[3]

Insurance carriers and health care planners have focused on services provided by different specialties and the providers of those services. As a result, frequently assuming a zero-sum economic model, they conclude that a redistribution of CMS-directed (Centers for Medicare & Medicaid Services) funding will result in more physicians in fields exhibiting shortages. They argue that managed competition, or a system like a staff-model health maintenance organization, would subsequently evolve to control costs, improve access, provide wellness services, and solve issues related to prevention.

Unfortunately, health care policy proposals based mostly on cost containment do not address issues of increasing technology, aging population, increased expectations of service, and the large number of uninsured, etc., which make some cost increases inevitable. Moreover, these proposals ignore the critical and worsening shortages of

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health care workers, of which some categories are already in critical shortage.

Unless addressed immediately, the shortage of appropriately trained health care providers will be in insufficient supply to implement the breadth and depth of modern medicine.

Substantial reform within the context of our current system is needed. We do not advocate scrapping the entire system and building anew, but rather saving the elements that have enabled its excellence. As interrelated critical elements, all participants in health care including patients, family doctors, surgeons, nurses, allied health professionals, insurers, state and federal governments, hospitals, academic medical centers, and professional societies must work to collaborate, cooperate, and clarify roles and expectations.

Insurance carriers and health planners have focused on cost. They frequently conclude that redistribution of CMS-directed funding within a zero-sum economic model will result in more physicians in fields of short supply. In the background is the seemingly wistful hope/belief that managed competition, or a system like a staff-model health maintenance organization, could evolve and control costs, improve access, provide prevention, and improve access to care for all Americans. This is not self-evident nor does research support the ability of a deceptively simple financial model to answer in practice the questions we expect of it in theory.

The health care system is fundamentally made up of people: patients, physicians, nurses, service providers, volunteers, educators, caretakers, policy makers, administrators, and infrastructure support personnel. Plans to reform it must support each and every component in order to attain improvements in quality care and reasonable access, as well as to cope with affordability and constraining costs. Surgeons are understandably one of these key components and, as such, are committed to partnership with others. A plan of reform that can result in real improvements while best balancing the needs of the public, patients, and service providers is needed.

White House conferences on health system reform have occurred, but to date, are mostly public relations events. The agenda for reform should include: (1) health care workforce shortage and supply, (2) universal coverage and access, (3) payment reform, (4) insurance and financing reform, (5) universal participation, (6) cost of proposed reforms, and (7) self-sufficiency of the United States in educating its domestic health care workforce.

The Workforce Shortage

In the 1920s, physicians comprised 25% of the health labor workforce. Today, physicians are 7%. The worsening health worker shortages are the salient concern for any reform plan. These shortages are problems of growing proportions, but they are not restricted to physicians. Shortages also exist for almost all types of health workers. The United States is projected to produce a demand to fill 5.3 million full-time health care jobs in all sectors between the years 2002 and 2012. Two million of these jobs represent turnover, but 3.3 million will be new jobs that address projected increases in demand for medical care.[4]

The co-existence of a physician shortage with shortages of registered nurses and other health workers presents a dangerous situation for the quality and availability of American health care. The proportional interdependence of a spectrum of health professionals is at the heart of an effective system of care. With these shortages promising to become worse, policy makers need to be prepared to support solutions that balance core resources.

The health worker shortages will be challenging to solve. In terms of reforming the system effectively, however, they are as critical to solve as affordability. Discussions about potential policy solutions must support the integration of the balance between physician and ancillary clinical practitioners. This is easy to overlook because of the ingrained fear that accelerating the supply of physicians and surgeons would endanger cost-containment objectives, a position that leads to rationing of health care. Yet, when data are illuminated about what is actually happening in the United States, a different picture emerges.

Medical Education+Residency: The Perfect Storm

The medical education "pipeline" begins with a 4-year baccalaureate degree, followed by 4 years of medical school leading to an MD or DO degree, with over 16,000 physicians graduating annually. These graduates from medical school then enter graduate medical education (GME) where they are joined by 5,000–7,000 International Medical Graduates (IMGs) to begin training in one of the 24 specialty fields of the Accreditation Council on Graduate Medical Education. After they have finished an average of 5 years of residency, leading to certification by one of the 24 American Board of Medical Specialties (ABMS) designated specialties, they enter practice and become health care providers in the United States.[5]

President John F. Kennedy initiated federal support directly to medical schools and stimulated their expansion from 88 to 126 in number, which increased the annual number of graduates from U.S. medical schools (USMGs) from 7,500 to near the current number of 16,000. President Lyndon B. Johnson's "Great Society" policies continued the expansionist period of medical education with the passage of Medicare in 1965, which included funding for GME. That support provided more funding for GME

positions than the number of USMGs and set the stage for the United States to rapidly expand its health workforce by training IMGs who enter the US on J-1 educational visas and remain in the United States for their medical careers.

It also became clear that advances in medical science stimulated the production of physician specialists. The family doctor of the future would be unable to encompass the breadth of practice provided by the general practitioner of the past who, through retirement, left gaps in covering the population's needs for a family doctor. The consensus followed that 50% of the physician workforce should be in "primary care." This objective was achieved by 1990 when 49% of certificates granted by the ABMS were in the primary care specialties of Family Medicine, Internal Medicine, and Pediatrics. However, the higher number of physicians receiving additional training in specialties limited the intended impact of a 50% primary-based workforce. The trend toward narrower, more focused practice, called progressive specialization, continues in all fields, including primary care.

In 1970, and during the following 20 years, it was believed by medical educators that a surplus of physicians was evolving and that the year 2000 would see a surplus of over 140,000 physicians.[6] In response, the medical education community self-imposed a moratorium on new medical schools leaving the number at about 126. By 2003, as it became apparent that, in fact, a shortage was evolving, the medical school community recommended an urgent program of expansion of medical schools and medical graduates. The present progress of expansion of about 13% more MDs is well on its way.

The "perfect storm" of the doctor shortage situation, which we face, is a voluntary fixed number of USMGs and a funding cap fixing the number of Medicare-funded residents, which Congress adopted in the Balanced Budget Act of 1997. As 32% of our current GME is filled by IMGs, the growth of medical school graduates will most likely just displace these IMGs with no net effect on increasing the number of physicians entering practice. So, the Balanced Budget Act of 1997 needs to be amended or revoked to allow support of GME, which is the final common pathway to practicing medicine in the United States.[7] Among the other confounding variables are population increase, scientific and technological breakthroughs, sub-specialization, changes in how people use physicians, and changes in the delivery system that have set aside managed care, capitation, and gatekeeper obstacles. The "senior surge" of the nation's 78 million baby boomers now reaching Medicare eligibility will stress the system further.

As this is a time of great change in the science of medicine, interventions that were unavailable even 5 years ago, require skill and training to implement these advances. The challenge extends to what education and training are necessary to competently provide the increasing spectrum of available interventions of modern medicine. Progressively specialized services are the evolving pattern of modern health care, coordinated with primary care services of a broad nature. It is essential that we focus the practice of our health care workers—physician and other—on the optimal use of their training. We should not utilize neurosurgeons or pediatric hematologists for annual check-ups or flu shots.

Primary Care Policy

Primary care is the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community.[8]

It is important to value the essential role of primary care services in health care, understanding that primary care is a service, not a specialty. The American Academy of Family Practice notes that many primary care services formerly provided by family doctors are now provided by physician extenders, of which the largest group is that of advanced practice nurses.[9] The American Association of Colleges of Nursing projects that 200 nursing schools will offer advanced practice degrees, and some already offer doctorates in primary care nursing. Advanced practice nurses have prescribing privileges in all states and are seeking a wider scope of practice in 24 states. They also wish to assume leadership roles in the CMS Medical Home demonstration projects.[10]

The service of primary care is at the core of the "medical home" movement, an organizational and financing system that is meant to enhance primary care services. The medical home model is not a replacement for primary care, but rather a system that supports that service through a financial mechanism (care management payments) and communications (information technology).

The contemporary medical home strategy resurfaces the system originally proposed by the Institute of Medicine in 1978. That proposal emphasized continuity and coordination between specialists and first-contact practitioners without specifying who would coordinate the care. Subsequently, related studies showed that specialists, especially surgeons when appropriate, were already providing continuity and coordination for patients—"primary care." Primary care is also being provided by advanced practice nurses in the context of complex specialty practices, such as transplantation and oncology. Such complex practices often require familiarity with unusual drugs, as well as knowledge of public and private insurance issues that are usually not in the training and skill set of a primary physician practitioner. The bulk of physician-based primary care is usually provided by specialty physicians from Family Medicine, Internal Medicine, and Pediatrics.[11] The largest number of residents is in internal medicine as a potential source of generalists. Unfortunately, only 2% plan careers in primary care.

In the foreseeable future, it is not possible for enough primary care physicians to be trained to meet the current and/or projected demands for the full spectrum of primary care services needed. Moreover, the aging of the population means that physicians of all specialties will have to be knowledgeable in geriatric issues and the needs of older patients, a logical and natural deployment of primary care practitioners–internists or family practitioners by narrowing their focus to geriatrics. The evolving role of advanced practice nurses in primary care should be supported. Nurses are the largest group of health professionals in the nation, and their contribution to meeting the primary care needs of our population should be expanded (Fig. 1).

All Physicians Do Not Provide Interchangeable Services

Many health planners examine physician population ratios and attempt to discern if sufficient densities of physicians exist in different states or regions. This simplistic approach ignores the fact that all physicians are not trained to provide the same service.

Along with surgeons from other fields, general surgeons are in serious shortage. Prudently accelerating the number of graduates is requisite to preventing the escalating costs inherent when the population's need for general surgery cannot be met in the community.

Some specialty fields, especially those in surgery, have little overlap; for example, a urological surgeon and a neurosurgeon provide vastly different services. The specialty of surgery with the broadest scope of practice, general surgery, fills a primary role in many communities, but that role can be assumed only with training in general surgery.[12]

Some specialties are in greater shortages than others. Generalist specialists, such as general surgeons, are especially in short supply because those services are increasingly in demand, and the number of general surgeons finishing education remains at about 1,000/year, a number that is unchanged since 1980. Specifically, the American Board of Surgery (ABS) certified 1,047 surgeons in 1981 and 1,032 in 2000 (Data courtesy of Dr. Tom Biester, ABS).

Great progress has been made in surgical sciences in the past 20 years. Surgeons in the US perform between 30–40 million operations annually. The technological and biological advances of surgical techniques that are employed in the therapy of diseases are ubiquitous. The commonest diseases of the twenty-first century—heart disease, cerebrovascular disease (stroke), cancer, and accidents are treated in many instances with surgery. Among the dramatic changes has been minimally invasive surgery. Over 80% of all gallbladder removals are done with a laparoscopic approach. Robotics, somewhat the successor to laparoscopy, is frequently employed in urologic surgery for removal of malignant prostates. In selected cases, cardiothoracic surgery is now performed with minimally invasive thorascopic technique. Resection of lobes of lungs for cancer is commonly performed with lessened morbidity than with the open techniques. Cardiovascular disease is predicted to continue to be the commonest cause of death in the twenty-first century, as it has been in the twentieth century. Unfortunately, cardiothoracic surgeons are becoming a scarcity as fewer complete training today than 10 years ago. In addition, with the current senior cohort of cardiothoracic surgeons in retirement mode, it is likely that insufficient numbers of cardiothoracic surgeons will be available. Similarly, fewer orthopedists are in training, and their senior surgeons are retiring also. Orthopedists replace hips, knees, and other joints that are common health issues for the elderly, affecting one in five Americans predicted to have arthritis in the twenty-first century (Fig. 2).

The population has increased by 25 million citizens in each of the last three decades. The output of surgical training programs has increased minimally, insufficient to

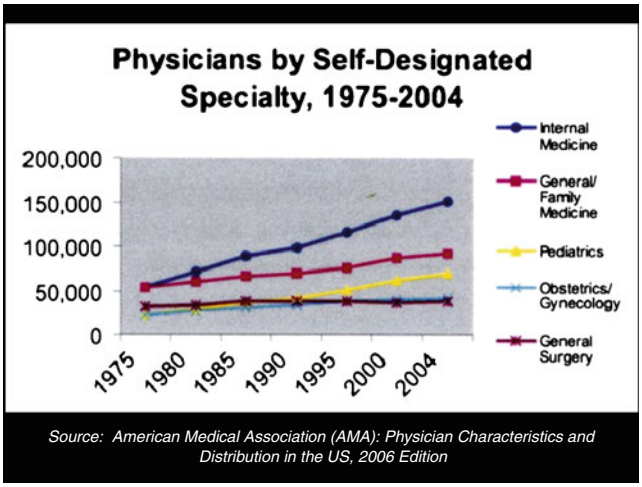

Fig. 1 Physicians by self-designated specialty, 1975–2004

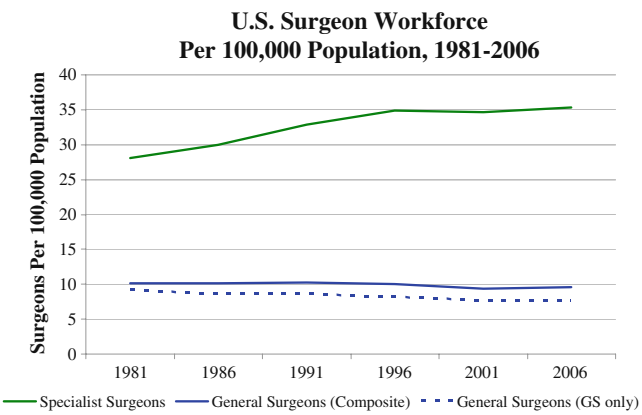

Fig. 2 U.S. surgeon workforce per 100,000 population, 1981–2006

keep up with population growth. Moreover, the percentage of elderly patients, with an average number of five chronic illnesses, will strain the health care system. In addition, the "senior surge" includes 78 million baby boomers who are now evolving into Social Security, and Medicare eligibility will require expanded health services.

Collaboration with other health professionals is expanding, but surgery remains an integral part of the management of most of the common diseases, often collaboration with other specialists. In the past 20 years, there has been little change in the number of graduates of any of the training programs in surgical fields, while technological advances in surgical technique, such as laparoscopic surgery, have thrust surgeons into treating a broader range of disease. Preventing and treating the leading causes of death today usually requires a surgeon at some point as integral to the treatment team or heading it. The health conditions that led to hospitalization in 2007, as identified by the Agency for Health Care Research and Quality, are arteriosclerosis (1,198,000), congestive heart failure (109,000), and chest pain (857,000). Certainly, the number of cardiovascular surgeons and cardiologists will need to be expanded. Collaboration among medical and surgical specialties is the hallmark of twenty-first century medicine.[13]

Moreover, 52 million Americans live in what are designated as rural areas. General surgeons are becoming increasingly rare in rural communities. In North Carolina, for example, 18 counties are without general surgeons, and many others have fewer general surgeons than 5 years ago. Often, the largest employer in a town, a rural community's hospital, is economically dependent on general surgical services for its viability.[14] In addition, retention of business and attracting new industry are difficult in a community without a spectrum of health care, which is often dependent on the presence of a general surgeon.[15]

The Health Workforce of the United States Is Impacted by the International Factor

The extent of the current workforce shortage is deceptive because meeting that demand is currently being managed by recruiting health care workers from the international community. Our dependency on international medical graduates is increasing. Currently, only 64% of practicing physicians in the United States graduated from American medical schools.[16] Likewise, foreign-educated nurses are easing the severity of the nursing shortage. According to the American Medical Association and the American Hospital Association (AHA), the countries of origin of these immigrant nurses are the Philippines (84%), Canada (33%), India (29%), and Africa (9%). As far back as 2001, the Special Workforce Survey, performed by the AHA, revealed that vacant positions for 126,000 health care jobs were unfilled. These jobs were for pharmacists, radiology technicians, billing coders, laboratory technicians, registered nurses, and maintenance personnel.[17]

In 2007, the World Health Organization declared a decade of challenge to address international workforce implications.[18] As the United States and other western nations struggle to meet workforce needs, they are recruiting physicians and nurses from less advantaged countries, thus, creating a "brain drain" that has raised concerns about international distributive justice. The United States should become self-sufficient in supplying its own health workforce.

Career Trends

There are only four residencies that have more applicants than positions. They are General Surgery, Plastic Surgery, Orthopedic Surgery, and Radiation Oncology. The more pronounced recent trend is a 51% fall in applicants to Family Medicine and a drop in applicant numbers to Internal Medicine. A *JAMA* paper in September 2008 revealed that only 2% of Internal Medicine residents planned to do primary care. Moreover, Internal Medicine is composed of 45% International Medical Graduates.

Analysis of the trends of the general surgery workforce between 1981 and 2005 showed that the number of general surgeons, relative to the population, declined by over 25% during that 25-year period. Even though the American population grew by more than 60 million people between 1981 and 2005,[14] the number of general surgeons actually declined by 4.2% over the same span of time. While this decline was felt in both rural and urban areas, rural areas continued to have significantly fewer general surgeons per capita than their urban counterparts. In 1981, only 39% of general surgeons were between the ages of 50 and 62; now, over 50% are between those ages. The American Board of Surgery certifies approximately 1,000 surgeons each year, a number unchanged since 1980. Whereas in 1992, a little over half of all general surgery residents entered a fellowship, now over 70% do so (Fig. 3).

General surgery is not alone among surgical specialties facing significant workforce challenges. The Dartmouth Atlas has compiled similar findings not only in general surgery but in other surgical specialties as well. Dartmouth data showed a 16.3% decline in the per capita number of general surgeons between 1996 and 2006, documenting per capita declines of 12%, 11.4%, and 7.1% in Urology, Ophthalmology, and Orthopedic surgery, respectively.

The health care provided by surgical services in the United States is essential; between 30–40 million operations are done annually. The implications of a surgical workforce shortage are currently under evaluation.

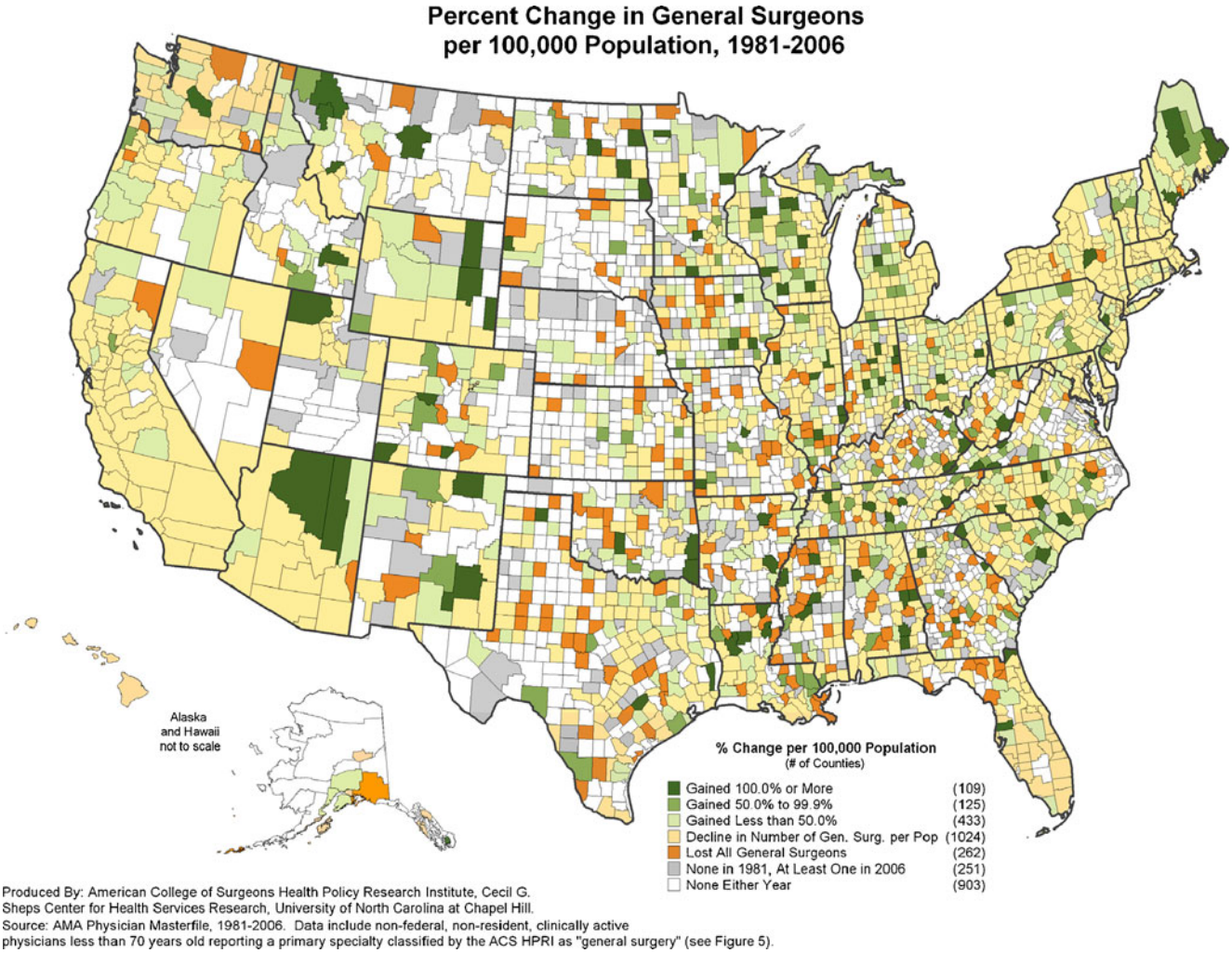

Fig. 3 Percent change in general surgeons per 100,000 population, 1981–2006

In 1981, the American Board of Surgery certified 1,047 and in 2008, 1,032. Approximately 70% take further training, called progressive specialization. The "super specialist" may result in limitation and scope of practice. Growth in the surgical workforce between 1981 and 2006 was fueled by an increase in physicians in surgical sub-specialty groups at the expense of general surgery. Only 4% (1,881) of the 46,451 net gain in surgeons in this 25-year period were general surgeons; an additional 3,349 (7.2%) were in specialties requiring prior certification in general surgery.

General surgery decreased as a proportion of the total surgical workforce from 24% in 1981 to 18% by 2006, reflecting both the slow growth of general surgeons and the expansion of several specialty groups, such as OB/GYN, Orthopedic, Plastic, and Thoracic Surgery.[19]

Lynge's study documented a 4% decrease in the number of general surgeons which, related to population, is a 27% decrease for urban areas and a 21% decrease in rural areas.[14]

Geography and Trends in Supply

Change in the geographic distribution of general surgeons was slightly worse than for all surgeons between 1981 and 2006. Approximately 41% of all counties experienced a declining ratio of general surgeons per 100,000 people, and a disproportionate number of those counties were urban. Whereas 34% (781) of rural counties had declining general surgeon to population ratios during the 25-year period, 60% (506) of all urban counties experienced declining ratios. Regional patterns of change in surgeon to population ratios for general surgeons did not mirror those for all surgeons. In every region of the country (and particularly in the northeast), more counties experienced declines in general surgeon to population ratios than experienced increases. Consistent with other findings, these data suggest that there has been a substantial loss of general surgeons across the

nation, and that this loss has been greatest in urban areas where surgical specialists have grown more rapidly.

Just under one quarter (709) of all counties had fewer surgeons per 100,000 residents in 2006 than in 1981. Approximately 82.2 million people (27.4% of the U.S. population) resided in these counties that experienced a decline in surgeon to population ratios in 2006. Regional variations in the gain or loss of surgeons show that counties in the northeast experience significant gains while losses were more common in the south.[19]

The decrease of general surgeons—and other surgeons—especially in rural America, is under analysis by the American College of Surgeons Health Policy Research Institute. Surgical services are essential for the existence of small communities. Moreover, the small town hospital is usually one of the largest employers in the town. As a health reform issue, attention should be directed on all elements of the health workforce. Specific assistance would be:

- Preserve Medicare funding for graduate medical education (GME) and eliminate the residency funding caps.
- Fully fund residency programs through at least the initial board eligibility.
- Include surgeons under the Title VII health professions programs, including the National Health Service Corps program, making them eligible for scholarships and loan assistance in return for commitment to generalist practice following training.
- Alleviate the burden of medical school debt and promote rural/underserved care through loan forgiveness programs that stipulate work in rural/underserved areas.
- Extend medical school loan deferment to the full length of residency training for surgeons.
- Allow young surgeons who qualify for the Economic Hardship Deferment to utilize this option beyond the current limit of 3 years into residency.
- Increase the aggregate combined Stafford loan limit for health professions students.

Conclusion

While there are many priorities for health care reform, primary goal is universal insurance coverage. To implement these mandates, we must enable having the right professionals in the right places to care for the patients of tomorrow. Achieving the goal of a high-quality health care system requires immediate attention to physicians, surgeons, nurses, and other health care providers now in short supply. Cost should be considered in the context of an aging population, the value of improved technology, and the projected impact of baby boomers entering Medicare eligibility. It should be understood that health care costs are likely to increase. The alternative is rationing. The challenge is to find revenue sources and payment methods and to maximize the efficiency and equity of the system.

The development of the new economies of China and India will in time make it more difficult for the United States to import the trained and talented physicians and surgeons we need. We have to look to our own resources to provide the health workers that are needed. Self-sufficiency in educating a prudent base of well-trained health care providers is urgently needed.

Expanding primary care service delivery and payment reform will not in themselves improve health care. Surgeons, now in shortage, provide unique services and are in short supply. We must balance our system and allow all the various components to share responsibility.

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2010 SSAT QUICK SHOT PRESENTATION

Functional Lumen Imaging Probe to Assess Geometric Changes in the Esophagogastric Junction Following Endolumenal Fundoplication

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Abstract
Background The functional lumen imaging probe (FLIP) uses impedance planimetry to measure the geometry of a distensible organ. The purpose of this study was to evaluate FLIP as a method to determine structural changes at the gastroesophageal junction (GEJ) following transoral incisionless fundoplication (TIF) and compare these findings with the accepted methods of esophageal testing.
Methods Two different approaches (TIF1.0 and 2.0) using the EsophyX™ device were performed in six and five animals, respectively. Three dogs underwent a sham procedure. FLIP measurements were performed pre- and post-procedure and at 2-week follow-up. Upper endoscopy, manometry, and 48-h pH testing were also performed at each time point. FLIP was performed in ten patients before and 3 months after TIF.
Results Following TIF procedures, there was a significant decrease in cross-sectional area (CSA) of GEJ compared to baseline; however, the CSA of both groups returned to baseline at 2-week follow-up. The FLIP results were supported with pH testing and correlated highly with both measures of GEJ structural integrity (LES and cardia circumference). Following TIF in humans, there was a decrease in GEJ distensibility compared to baseline that persisted to the 3-month evaluation.
Conclusion FLIP is able to measure and display changes in tissue distensibility at the GEJ, and results correlate with established methods of testing. FLIP may represent a single testing modality by which to diagnose GERD and evaluate the outcome after antireflux surgery.

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Keywords Gastroesophageal reflux · Functional lumen imaging probe · Endolumenal fundoplication · Antireflux surgery

Introduction

The functional lumen imaging probe (FLIP) uses impedance planimetry to measure the geometry of a distensible organ. The device includes a balloon catheter sensor connected to a data recorder and a display system (Fig. 1). Using a defined distension protocol, the balloon is filled with a saline solution at different volumes to determine the shape of the region as it resists this distention. By conversion of electrical impedance measurements into cross-sectional area (CSA), real-time dynamic images can be displayed and geometry data can be determined. The catheter is introduced along or through a therapeutic endoscope and positioned at the level of the gastroesophageal junction (GEJ). FLIP was shown to be effective in the determination of tissue mechanics in response to a radial challenge[1] and may contribute diagnostically in defining tissue behavior characteristics in specific diseases, such as gastroesophageal reflux disease (GERD). This new method may also be useful to assess the outcome of antireflux surgery.

Effective surgical treatment for GERD has to involve structural changes to the antireflux barrier at the level of GEJ. The surgical restoration of this barrier ideally should result in a competent one-way valve that enables the unobstructed passage of food from the esophagus into the stomach and reduce or inhibit the retrograde flow of solid and liquid gastric contents. If we accept that in some way this valve effect occurs by a narrowing in the junction, reduction of flow must be related to the squeezing or closing of the GEJ.[2,3] By using FLIP, there may be a measurable effect on tissue distensibility irrespective of "tightening," and the ability to determine the contributions of intrinsic and extrinsic components of the reconstructed valve. FLIP will also likely play a role in the assessment of failure after antireflux surgery.

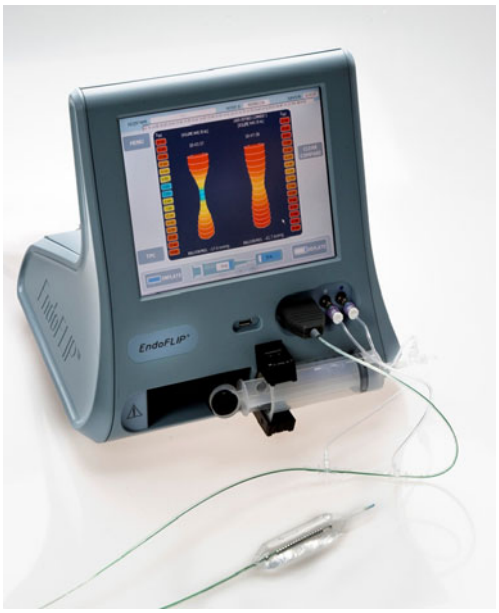

Fig. 1 The functional lumen imaging probe catheter and measurement system. Conductive solution is injected from the syringe into the balloon that surrounds the impedance electrodes and pressure transducers. Cross-sectional area is then calculated and displayed on the screen in real time for a given volume injected and balloon pressure (Image from Crospon Ltd., Galway, Ireland)

Transoral incisionless fundoplication (TIF) enables recreation of an antireflux barrier by enveloping the distal esophagus within the proximal stomach, using the deployment of transmurally placed polypropylene tissue fasteners. TIF has been shown to be effective in the reduction of esophageal acid exposure and improvement of lower esophageal sphincter physiology measures in canines[4] and in chronic GERD patients.[2,5]

This study was nested within an investigation that aimed to compare the short-term success of two approaches to TIF using the EsophyX™ device (Endogastric Solutions, Redmond, WA).[4] The canine model was chosen because the native GEJ is comparable to that of chronic GERD patients with a Hill classification grade III valve.[6–8] The purpose of this study was to evaluate FLIP as a method by which to determine structural changes at the GEJ following TIF and compare these findings with the accepted methods of objective esophageal testing.

Material and Methods

Functional Lumen Imaging Probe

The FLIP probe used in this study and the measurement protocol were similar to those previously described.[1] The probe consisted of a seven-lumen, 72-cm-long catheter with a 10-cm balloon that was compliant to an inflated diameter of 3.2 cm. Within the balloon, there were 16 electrode pairs with 1 mm distance between each electrode within a pair and a distance of 4 mm between each pair. Based on this electrode array, the probe measured eight evenly spaced CSAs over a 28-mm longitudinal distance across the GEJ. In a distension protocol, an infusion pump filled the catheter balloon with a saline solution (0.022 ml/mg) at a flow rate of 40 ml/min and to a maximum volume of 50 ml. By conversion of electrical impedance measurements into CSA, FLIP provides real-time images of CSA over the entire GEJ throughout the period of balloon filling.

Study Design

FLIP measurements were performed in 14 dogs under the regulations of the Animal Care and Use Committee at the Hope Heart Institute (Bellevue, WA). After instituting general anesthesia, upper endoscopy was performed to inspect the GEJ and obtain endoscopic images of the GEJ for the software-based measurement of cardia circumference. The FLIP probe was inserted and positioned across the GEJ under endoscopic guidance (Fig. 2). Pre-procedure FLIP measurements were obtained at three different balloon distension volumes (40, 50, and 60 ml). Three complete balloon fills were obtained for each animal.

Eleven dogs underwent TIF using the EsophyX™ device. Two techniques, TIF1.0 and TIF2.0, were compared in this study.[4] The TIF1.0 procedure involves the deployment of fasteners more centrally on the greater curvature side to create an omega-shaped valve of >220° by gastrogastric plication. In the TIF2.0 procedure, the fastener deployment is initiated on the far posterior and anterior sides adjacent to the lesser curvature to create a nipple valve of >240°. Then, by deploying fasteners between the distal esophagus and stomach, gastroesophageal plication is performed.

The animals were randomly assigned to an experimental group (or sham) and underwent either TIF1.0 (n=6) or TIF2.0 (n=5). Three dogs had a sham intervention, in which the device was introduced and tissue was retracted and clamped with the tissue mold, but stylets and fasteners were not deployed. Immediately following the procedure or sham, the FLIP probe was repositioned across the GEJ under endoscopic guidance, and the measurements were repeated; finally, FLIP was repeated at 2 weeks post-procedure. A total of three FLIP measurements were performed for each animal at each time point. Dogs were fed a liquid diet for the first 3 days after the procedure and then given canned soft food for the remainder of the study.

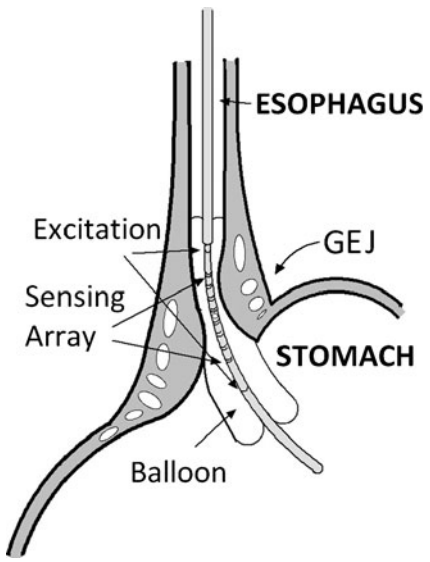

Fig. 2 The FLIP probe placed across the gastroesophageal junction

Upper endoscopy, high-resolution manometry, and 48-h distal esophageal pH monitoring were performed at each time point in every animal in order to examine the impact of TIF on GEJ structure and function. Briefly, the objective testing was performed using the following protocols:

1. *Upper endoscopy*: Animals underwent endoscopic valve grading and assessment using established criteria.[9,10] Hill Classification and cardia circumference were obtained from digital images at each time point. All images were measured using a validated software package.[11]
2. *High-resolution manometry* was performed using a solid-state assembly with 36 circumferential sensors spaced at 1-cm intervals (ManoScan, Sierra Scientific Instruments, Inc., Los Angeles, CA) to determine the lower esophageal sphincter pressure (LESP). Resting LESP was obtained during a period of quiescence and calculated as the mean pressure over the entire length of the distal high-pressure zone using the "sleeve" software function.
3. *48-h pH monitoring* was performed using a "wireless" pH probe (Bravo pH System, Medtronic, Minneapolis, MN). The pH capsule was attached to the esophageal mucosa 6 cm proximal to the endoscopically measured GEJ and left in place for 48 h. The probe transmitted pH values to an external recorder.

Software-Based Measurements of Cardia Circumference

The circumference of the gastric cardia in static retroflexed endoscopic images was measured by using a software package, which was developed using Flash (Macromedia Inc., San Francisco, CA) on the Windows 2000 platform (Microsoft Inc., Redmond, WA).[11] Images were imported from the endoscopic record into the software program. To calibrate the measurement system, the examiner outlines the endoscope shaft at the point where it enters the stomach at the level of the cardia. The examiner then positions and sizes a circle on the image that approximates the diameter of the cardia along the inner rim of the orifice at the junction between the esophagus and stomach. By using the known diameter of the endoscope, the software calculates the circumference of the cardia on the basis of the relative sizes of the circles.

FLIP Measurements in Humans Undergoing TIF

FLIP was performed in ten patients before, immediately following, and 3 months after TIF. Patient selection was

based on the presence of chronic GERD confirmed by pH testing, minimal (<2 cm) or no hiatal hernia, and a normal or hypotensive lower esophageal sphincter (LES). The FLIP catheter was inserted orally, positioned across the GEJ, and the balloon was inflated three consecutive times. The balloon was completely deflated between distensions. FLIP measurements were collected to evaluate the effects of TIF procedure on the GEJ.

Data Analysis

Mean and standard deviation (SD) of CSA, DeMeester score (DMS), LESP, and cardia circumference were calculated for each animal and group. The smallest CSA over the entire catheter was chosen as the basis for comparison at a 50-ml balloon fill. A paired t test was used to compare changes in all data endpoints from baseline to immediate post-procedure and 2-week follow-up time points, respectively, within each group. A p value <0.05 was considered to be statistically significant. Correlation coefficient (r) was calculated to assess the presence of a linear relationship between the FLIP measurements and other objective testing including pH monitoring, manometry, and endoscopic cardia circumference measurement ($0<r<\pm0.25$, no or low degree of correlation; $\pm0.25<r<\pm0.75$, moderate degree of correlation; $\pm0.75<r<\pm1$, high degree of correlation). All values of each measurement method regardless of time points and groups were included to calculate correlation coefficient in order to evaluate a relationship between each measurement method.

Results

Objective Testing as the Current Gold Standard to Assess Outcome of TIF

TIF2.0 reduced DMS immediately post-procedure; however, at 2-week follow-up, esophageal acid exposure had increased back to baseline values. Compared to baseline, there was no significant decrease in DMS at either time point after TIF 1.0 ($p=0.2$ and $p=0.68$, respectively). Similarly, the sham intervention had no impact on DMS compared to baseline scores (Fig. 3a).

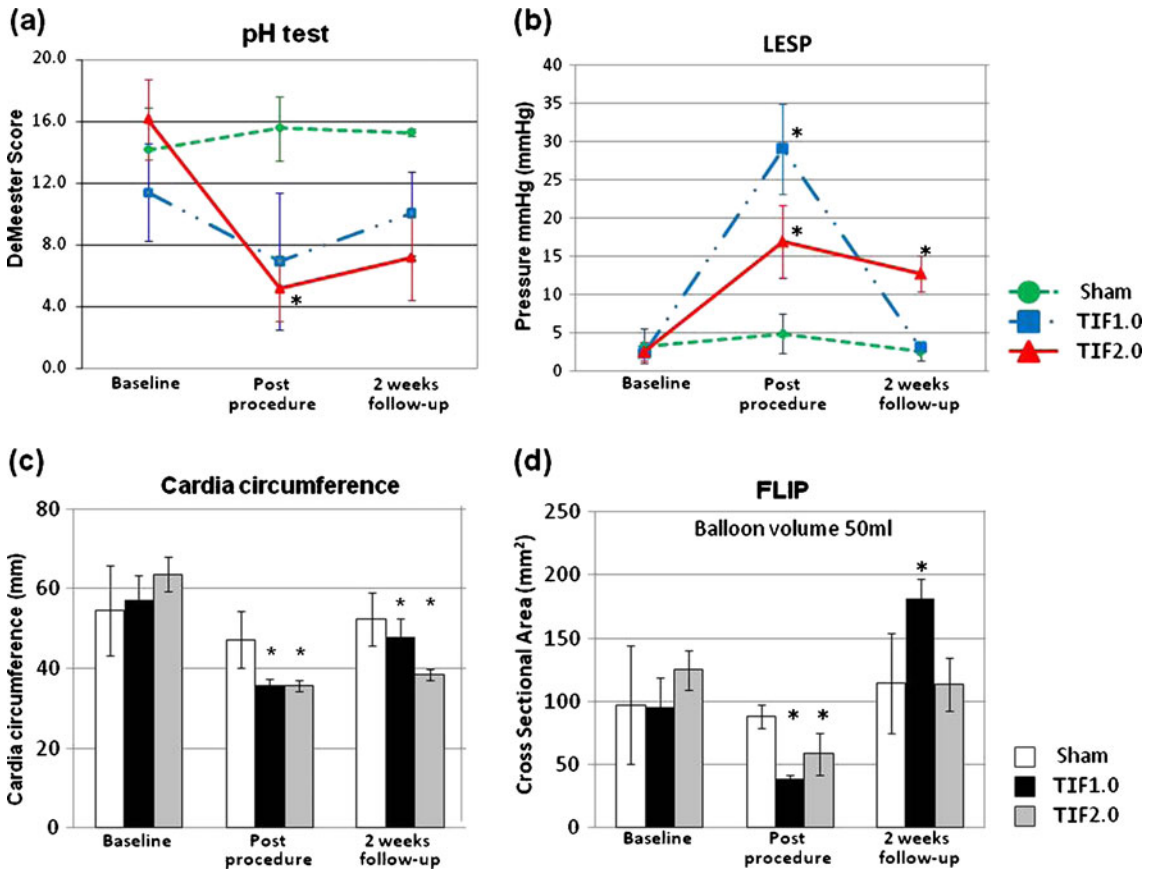

Fig. 3 DeMeester score (**a**), lower esophageal sphincter pressure (**b**), cardia circumference (**c**), and FLIP (**d**) at each time point within each group. $*p<0.05$ compared to baseline measurement

There was a significant increase in resting LESP immediately after both TIF procedures. However, the LESP for TIF1.0 was not durable and returned to baseline at 2-week follow-up, indicating valve failure. Although it decreased from immediate post-procedure values, the LESP for TIF2.0 remained significantly increased compared to baseline (p=0.006). In the sham group, there was no change in the pretreatment LESP at either time point (p=0.058 and p=0.59, respectively; Fig. 3b).

In conjunction with a decrease in DMS and an elevation in LESP, there was a significant decrease in cardia circumference for both TIF1.0 and TIF2.0 groups from baseline to immediate post-procedure and 2 week follow-up. In the sham group, there was a slight decrease in cardia circumference from baseline to immediate post-procedure (p=0.39), but not from baseline to 2-week follow-up (Fig. 3c). Compared to the FLIP measurements, all other measurement methods showed a similar, strong tendency that tissue resistance was increased in both TIF1.0 and TIF2.0 groups from baseline to immediate post-procedure, but returned to the baseline or decreased at 2-week follow-up (Fig. 3).

FLIP as a Measure of TIF Outcome

The use of FLIP for assessment of the GEJ was feasible in all animals, and no adverse events occurred as a result of insertion or balloon distension. With serial increases in balloon volume, FLIP successfully demonstrated tissue distensibility across the GEJ (Fig. 4). The relationship between increases in balloon volume and CSA demonstrated that GEJ distensibility was significantly decreased from baseline after both TIF1.0 and TIF2.0 procedures (p=0.035 and p=0.033, respectively). However, at 2-week follow-up, distensibility had increased significantly beyond baseline (TIF1.0, p=0.002) or returned to baseline (TIF2.0, p=0.67; Table 1). The sham intervention had no effect on GEJ distensibility at either time point. These findings strongly support the combined results of objective testing as a determinate of TIF repair integrity. FLIP data could be

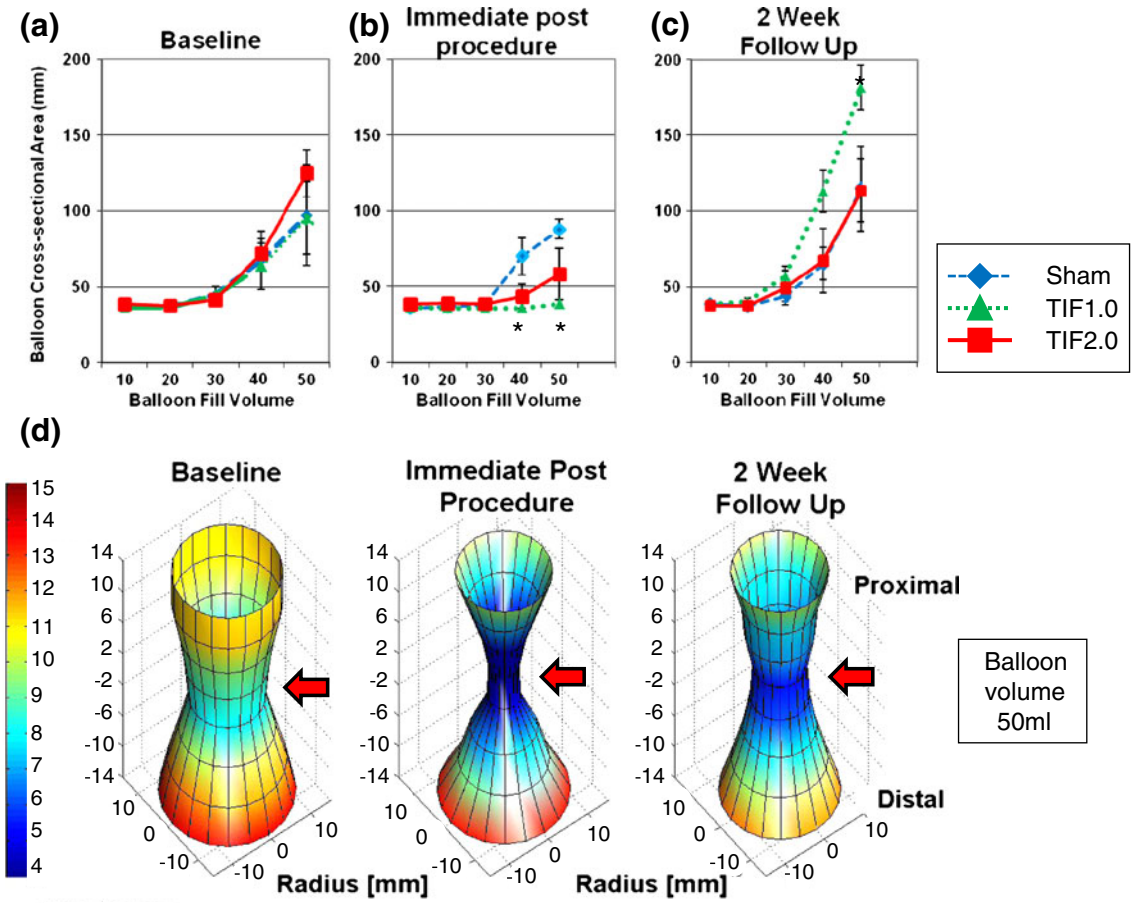

Fig. 4 The relationship between the balloon fill volume and the narrowest CSA measured for Sham, TIF1.0, and TIF2.0 at baseline (**a**), immediately post-procedure (**b**), and at 2-week follow-up (**c**). GEJ distensibility returns to baseline (TIF 2.0) or exceeds baseline (TIF1.0) at 2-week follow-up. The three-dimensional data of FLIP displayed the shape of the balloon at the level of GEJ (**d**). *Red arrows* illustrate the narrowest CSA for each measurement. *CSA* cross-sectional area, *TIF* transoral incisionless fundoplication, *FLIP* functional lumen imaging probe, *GEJ* gastroesophageal junction

Table 1 Outcome measures (mean and standard deviation) at each time point within a group

	Baseline	Postprocedure	*p* value	2 weeks follow-up	*p* value
Sham (*n*=3)					
LESP	3.23 (3.90)	4.87 (4.54)	0.058	2.53 (2.03)	0.59
DMS	14.17 (7.25)	15.57 (5.50)	0.33	15.27 (0.61)	0.82
CC	54.5 (19.7)	47.2 (12.4)	0.39	52.4 (11.5)	0.84
CSA	97.34 (80.9)	88.08 (15.6)	0.54	114.89 (68.4)	0.818
TIF1.0 (*n*=6)					
LESP	2.32 (0.69)	29.1 (14.37)	*0.003	3.08 (1.41)	0.352
DMS	11.4 (8.30)	6.95 (11.6)	0.207	10.07 (7.18)	0.682
CC	57.3 (14.7)	35.9 (3.79)	*0.006	48.0 (11.4)	*0.014
CSA	95.32 (58.7)	38.94 (7.20)	*0.035	181.77 (36.6)	*0.002
TIF2.0 (*n*=5)					
LESP	2.56 (2.57)	16.93 (9.62)	*0.043	12.76 (5.29)	*0.006
DMS	16.2 (6.86)	5.2 (5.48)	*0.0004	7.2 (7.22)	0.076
CC	63.7 (9.46)	35.6 (3.30)	*0.001	38.5 (3.13)	*0.002
CSA	124.99 (37.9)	58.52 (37.8)	*0.033	113.53 (50.9)	0.672

LESP LES pressure (millimeters mercury), *DMS* DeMeester score, *CC* cardia circumference (millimeters), and *CSA* (square millimeters) SD of the EGJ at a 50-ml balloon fill at baseline, immediate post-procedure, and 2-week follow-up after TIF

*$p<0.05$ compared to baseline measurement

displayed as extrapolated three-dimensional images along the length of the balloon that supported the electrode pairs. The three-dimensional data obtained from FLIP enabled "imaging" of the GEJ by visually imparting tissue behavior in response to a radial challenge (Fig. 4).

Correlation Between Objective Testing and FLIP Results

There was a highly significant inverse correlation between FLIP-generated CSA measurements and LESP ($r=-0.50$; $p<0.001$; Fig. 5a). Additionally, there was a highly

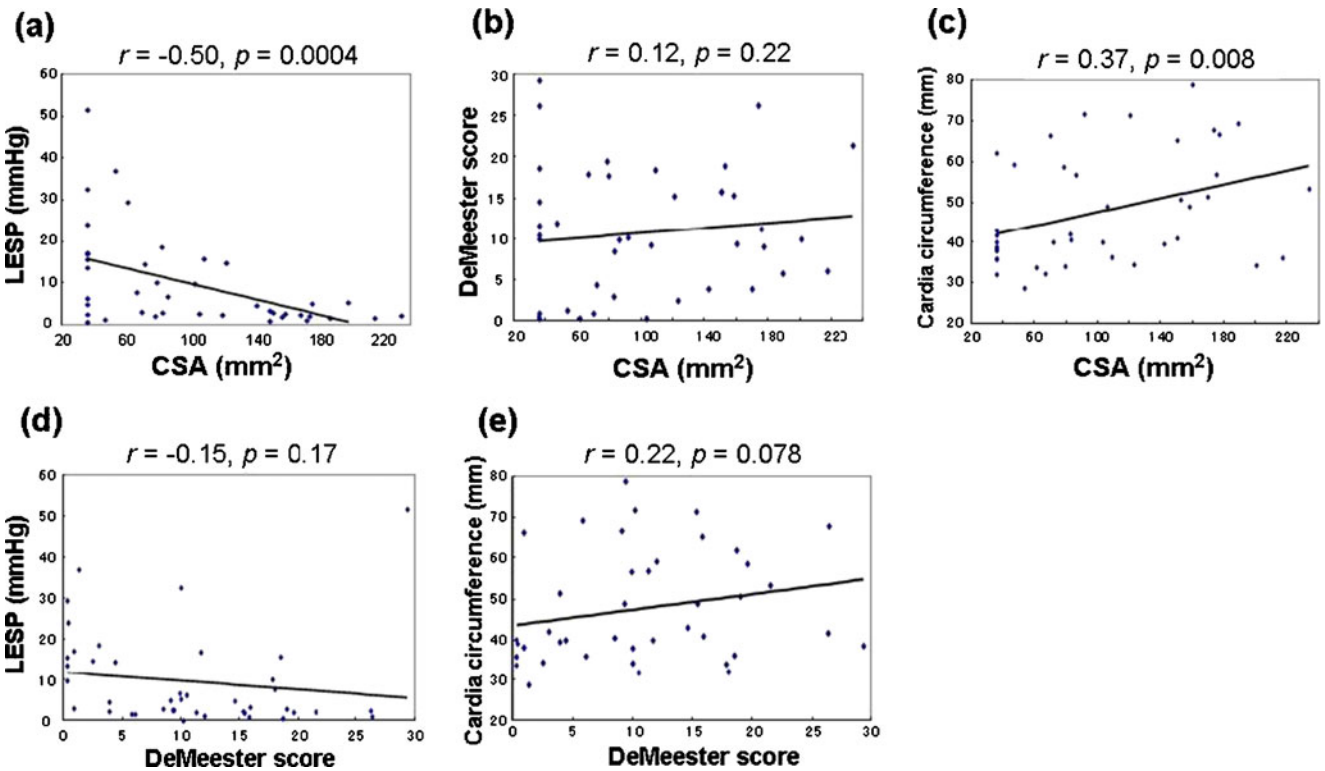

Fig. 5 Correlations between FLIP data and other methods of objective testing. **a** FLIP vs. lower esophageal sphincter pressure (LESP), **b** FLIP vs DeMeester Score (DMS), **c** FLIP vs. cardia circumference, **d** DMS vs. LESP, and **e** DMS vs. cardia circumference. There is no correlation between DMS and FLIP or conventional measures of barrier integrity. Correlation coefficient (r) and p value were calculated ($0<r<\pm0.25$, no or low degree of correlation; $\pm0.25<r<\pm0.75$, moderate degree of correlation; $\pm0.75<r<\pm1$, high degree of correlation). A p value <0.05 was considered to be statistically significant

significant degree of positive correlation between FLIP-generated CSA measurements and cardia circumference (r=0.37; p=0.008; Fig. 5c). DMS did not correlate with FLIP-derived measurement of CSA (r=0.12; p=0.22; Fig. 5b). Similarly, DMS did not correlate with LESP or cardia circumference (r=−0.15, p=0.17 and r=0.22, p=0.078, respectively; Fig. 5d, e). Despite this, DMS clearly reflected the structural failure and resultant incompetence of the TIF valves at 2-week follow-up (Fig. 3a).

Human FLIP Measurements Before and After TIF

Ten patients (two male and eight female, age 32–63) underwent TIF, and there were no complications related to catheter placement or balloon distension. With serial increases in balloon volume (10–60 ml), FLIP successfully demonstrated tissue distensibility across the GEJ (Fig. 6a). The relationship between increases in balloon pressure and CSA demonstrated that GEJ distensibility was significantly

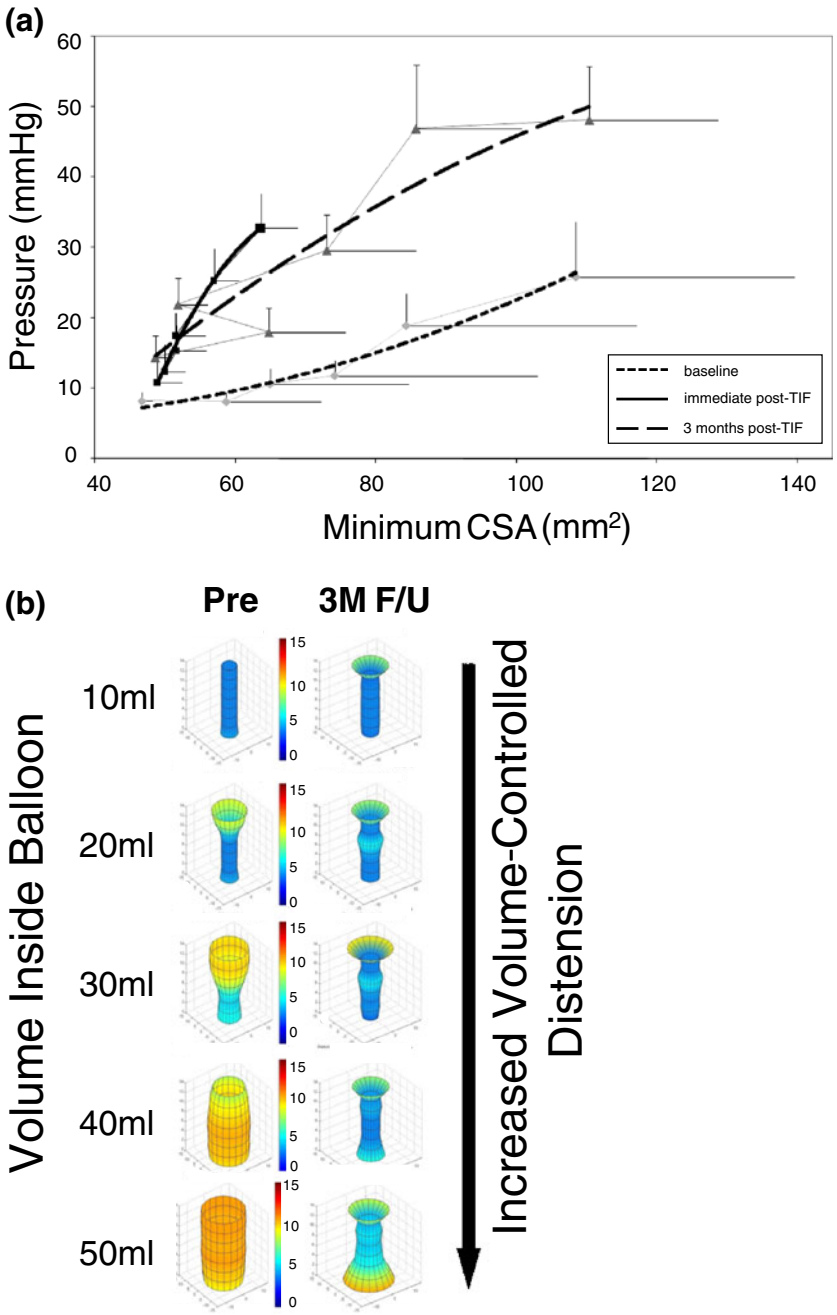

Fig. 6 **a** The mean pressure versus GEJ cross-sectional area (CSA) for all patients at balloon volumes of 10, 20, 30, 40, 50, and 60 ml. The *thick black lines* (*small dashed*, *solid*, and *large dashed*) represent the best polynomial second-order fit for the data at baseline, immediate post-TIF, and 3-month follow-up, respectively. **b** Three-dimensional reconstruction of GEJ in a patient before and 3 months following TIF. CSA was tested at balloon volumes of 10, 20, 30, 40, 50, and 60 ml

decreased in humans after the TIF procedure. Immediately after TIF, the GEJ exhibited very little change in CSA over the range of balloon pressures, suggesting tissue rigidity; however, at 3 months post-procedure, GEJ distensibility had increased but was still less than baseline values. Data could be displayed as extrapolated three-dimensional images along the length of the balloon and suggested that the TIF repair was intact at the 3-month evaluation (Fig. 6b).

Discussion

There is a need to better understand tissue mechanics as it relates to the pathophysiology of GERD. The results of the present study suggest that FLIP can be used to determine GEJ distensibility prior to and after intervention, and that these data can be interpreted to determine the status of repair integrity and function. Unlike esophageal manometry, which consists of static intralumenal pressure measurements, FLIP enables assessment of tissue distensibility in response to a radial challenge, and this represents potential "superiority" over existing esophageal testing modalities. We hypothesize that an intimate understanding of tissue distensibility will serve as a measure of barrier function in health and disease. This is the first investigation to compare and correlate the results of conventional multimodality testing with those of FLIP.

Using the currently accepted gold standard for objective testing of the GEJ, TIF resulted in an immediate post-procedure "tightening" of the valve that loosened within 2-week follow-up. The LES resting pressure, endoscopic examination, and cardia circumference measurement supported these findings, and pH data confirmed an initial augmentation in valve competency, particularly in animals that underwent TIF2.0. Correlating with the reduction in LESP at 2-week follow-up, esophageal acid exposure had increased in both groups at 2 weeks.

FLIP measurements did not register a change in distensibility at any time point until a balloon volume of 30 cc was reached, highlighting the patulous nature of the canine cardia. Based on this finding, we elected to compare differences in CSA at a balloon fill of 50 ml. Immediately post-procedure, we observed a significant reduction in tissue distensibility in both treatment groups, indicating that the proximal stomach had enveloped the distal esophagus, cradling the GEJ with two additional wall layers of intestine. Based on the technique, there is also circumferential tightening created by the plication, leading to an additional reduction in distensibility and thus CSA compared to the sham. FLIP results correlated with those of conventional testing, thereby supporting the validity of this testing modality.

Tissue distensibility had returned to baseline levels by 2-week follow-up, and conventional testing suggested that the TIF repairs had either partially or completely failed. Dogs typically have a Hill classification grade III valve and do not have the presence of a hiatal hernia. Therefore, the canine cardia is structurally amenable to create an antireflux valve. However, regurgitation is a normal, adaptive behavior in dogs, and canines are not an ideal model for assessing long-term efficacy of antireflux procedures[14] because of the post-procedural stresses placed on the repair, resulting in disruption of a newly created valve.

In fact, animals that underwent the TIF1.0 approach had a significant *increase* in distensibility compared to baseline. This unexpected change in tissue mechanics was not observed by conventional testing (e.g., cardia circumference<baseline and LESP=baseline) and suggests that TIF1.0 animals were less likely to resist reflux events 2 weeks after the procedure when compared to pre-procedure values; this finding was supported by a return of DeMeester score to the pre-procedure value at 2-week follow-up.

In animals that underwent the TIF2.0 approach, DeMeester score and CSA measurements had returned to baseline levels by 2-week follow-up, suggesting the failure of TIF2.0 repair. However, LESP remained significantly increased even at 2-week follow-up compared to pre-procedure values. The LESP, which represents a static intralumenal pressure measurement, may not lend sufficient insight to determine valve integrity/competency—resting LESP does not tell the whole story as there is no "challenge" placed on the surrounding tissue with balloon inflation. That being said, while the LESP remained elevated at the 2-week time point, it was trending back towards pre-procedure values. In light of the increased distal esophageal acid exposure in this group, these findings suggest that FLIP may potentially provide a more accurate assessment of repair integrity across the GEJ by enabling one to "factor out" confounding issues such as intralumenal edema or scarring that may lead to misleading findings.

It is likely that FLIP represents a modality by which to assess the structural integrity of the human GEJ. The human data indicated that FLIP demonstrated the change of tissue compliance at the GEJ after TIF and could be a useful tool to evaluate the effects of antireflux procedures at the GEJ. In other human pilot work, Kwiatek and colleagues established that GEJ distensibility is two- to threefold higher in GERD patients compared to controls.[12] This likely reflects the attenuation and stretching of the collar sling musculature that leads to a defective barrier.[13] Even though FLIP demonstrated increased distensibility of the GEJ, there appears to be heterogeneity amongst GERD patients, and this may ultimately limit its use as a "one stop" testing modality that definitively reflects barrier status

in all patients. Future studies with long-term follow-up will be required in order to gauge clinical applications of FLIP.

In conclusion, the use of the FLIP was feasible and safe in a canine model and humans of endolumenal fundoplication. With FLIP, we were able to consistently measure and display tissue distensibility over a range of balloon volumes at the level of GEJ following the TIF procedure. FLIP correlated highly with LESP and cardia circumference, and these findings were supported with pH testing. FLIP may compliment and/or replace accepted methods of objective esophageal testing to diagnose GERD and to evaluate outcome after surgical procedures of the esophagus and hiatus.

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ORIGINAL ARTICLE

A Comparison of Pre-operative Comorbidities and Post-operative Outcomes among Patients Undergoing Laparoscopic Nissen Fundoplication at High- and Low-Volume Centers

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Abstract
Introduction Commonly cited data promoting laparoscopic Nissen fundoplication (LNF) as safe and efficacious are typically published by single centers, affiliated with teaching institutions with a high volume of cases, but LNF is not universally performed at these hospitals. The purpose of this study is to assess where these procedures are being done and to compare pre-operative comorbidities and post-operative outcomes between high-and low-volume centers using a state-wide inpatient database.
Methods This is a retrospective study using data from the North Carolina Hospital Association Patient Data System. Selected patients include adults (>17 years old) that have undergone laparoscopic Nissen fundoplication for gastroesophageal reflux disease as an inpatient from 2005 to 2008. Patients that underwent operative management for emergent purposes or had associated diagnoses of esophageal cancer or achalasia were excluded from the study. High-volume centers were defined as institutions that performed ten or more LNFs per year averaged over a period of 4 years. Comparative statistics were performed on comorbidities and complications between high- and low-volume centers.
Results A total of 1,019 patients underwent LNF for GERD in North Carolina between 2005 and 2008 in the inpatient setting. High-volume centers performed 530 LNFs (52%) while low-volume centers performed 489 LNFs (48%). Patients at high-volume centers were older (median 52.5 years old vs. 49.0 years old, $p=0.019$), had a higher incidence of diabetes (13.4% vs. 8.8%, $p=0.026$), chronic obstructive pulmonary disease (5.1% vs. 2.0 %, $p=0.015$), hyperlipidemia (9.6% vs. 4.7%, $p=0.004$), and cystic fibrosis (2.8% vs. 0.8%, $p=0.03$). Patients with a history of transplantation were also more likely to undergo LNF at a high-volume center (15.8% vs. 1.6%, $p<0.0001$). There were no deaths among the two groups and also no difference between median length of stay (2.7 days for high-volume center vs. 2.6 days for low-volume center). Low-volume centers had a higher incidence of intraoperative accidental puncture or laceration (3.3% vs. 0.9%, $p=0.017$) while high-volume centers had a higher incidence of atelectasis (5.3% vs. 2.5%, $p=0.031$).
Conclusion A significant proportion of the LNFs in North Carolina are performed at low-volume centers. High-volume centers perform LNF on older patients with more comorbidities. Low-volume centers have three times more accidental perforations, yet there is no detectable difference in mortality or median length of stay. It is impossible to tell if these perforations are managed at these low-volume centers or transferred to facilities with a higher level of care. These findings argue for regionalization of LNF and for a reevaluation of the global safety of this operation.

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Introduction

Laparoscopic Nissen fundoplication (LNF) has become the most commonly performed antireflux procedure since its

introduction in 1991 by Dallemagne et al.[1] Between 1990 and 1997, the annual rate of antireflux surgery increased from 4.4 to 12.0 per 100,000 with the proportion of antireflux procedures performed laparoscopically increasing from 0.5% to 64%.[1] The growth in popularity can be attributed to the published success of surgery as compared to medical therapy as well as the acceptance of the minimally invasive approach.[2] Favorable reports of outcomes from LNF tend to emanate from single centers and academic institutions that perform a large volume of cases.[2–6]

However, as this operation grew in popularity, it was performed at a wide variety of institutions and had the potential to produce results inconsistent with those proposed by peer review publications. Analyses of morbidity and mortality of failed antireflux surgery highlight the importance of proper patient selection and surgical technique.[7–9] LNF is a technically challenging procedure and even minor variations in surgical technique can alter clinical outcome.[10,11] Moreover, LNF has a well-defined learning curve with failures that typically occur during the initial learning phase.[8,10–12] Failure of primary LNF is infrequent if performed by an experienced surgical team and results of redo LNF are not as good, further exemplifying the importance of proper surgical technique and experience.[7]

Population-based outcomes assessment has played a synergistic role with the evolution of minimally invasive surgery as it has helped shape practice patterns and impact decision-making.[13] Acceptance of LNF has been driven by outcome-based comparisons between open and laparoscopic procedures, which have demonstrated benefits of minimally invasive surgery with respect to length of stay, pain, costs, morbidity, mortality, and overall patient satisfaction.[14–18] Conversely, outcome assessments can also be used to demonstrate shortcomings of laparoscopic surgery and thus further refine technique or patient selection to ultimately improve patient care. The development of state-wide and nationwide databases have aided in this endeavor as they provide benchmarks against which both academic and community surgeons can compare themselves.[13]

The purpose of this study is to assess where LNFs are performed and to compare pre-operative comorbidities and post-operative outcomes between high- and low-volume centers using a state-wide inpatient database.

Patients and Methods

Data Sources

This is a retrospective study using data from the North Carolina Hospital Association Patient Data System (NCHA PDS). The NCHA PDS has collected select data elements required by the State of North Carolina Medical Care Data Act since 1995. The data source is administrative from licensed hospitals. Thomson Reuters is certified by the State to collect the data in compliance with the Act. Data are used for public health, research, State health planning, and hospital quality and patient safety initiatives. NCHA PDS includes a total of 62 state-wide hospitals from both teaching and community institutions. It includes only anonymous data from inpatient discharge information without unique identifiers.

Inclusion and Exclusion Criteria

Selected patients included adults (>17 years old) that have undergone laparoscopic Nissen fundoplication for gastroesophageal reflux disease (GERD). The database was queried by International Classification of Diseases, ninth revision (ICD-9) procedure code 44.67 (LNF) with the primary diagnosis code of 530.81 (GERD) between 2005 and 2008. Prior to 2005, the ICD-9 code for LNF did not exist. Patients that underwent operative management for emergent purposes or had associated ICD-9 diagnosis codes of esophageal cancer (150.0–150.5 and 150.8–150.9) or achalasia (530.0) were excluded from the study. High-volume centers were defined as institutions that performed ten or more LNFs per year averaged over a period of 4 years.

Outcomes

Patient age, gender, comorbidities, hospital length of stay (LOS), complications, and deaths were examined. Comorbidities included Barrett's esophagus, hiatal hernia, esophageal stricture, esophageal dyskinesia, obesity, coronary artery disease, atherosclerosis, myocardial infarction, diabetes, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, central nervous system disease, tobacco abuse, vascular disease, asthma, adhesions, gastroparesis, transplant, hyperlipidemia, cystic fibrosis, obstructive sleep apnea, and neoplasm. Complications included wound hematoma, seroma, abscess, pulmonary embolism, sepsis, deep venous thrombosis, aspiration, pneumothorax, accidental puncture or laceration, pulmonary collapse or atelectasis, transfusion of blood products, respiratory arrest, hemorrhage complicating a procedure, infection, and respiratory, cardiac, digestive system, central nervous system, or urinary complications not elsewhere classified. Comorbidities and complications were defined by ICD-9 diagnoses codes following the Agency for Healthcare Research and Quality definitions.

Statistical Analysis

Comparative statistics (*N* (percent) or mean, SD, median, range) were performed on comorbidities and complications

between high- and low-volume centers. Wilcoxon rank–sum tests or *t* tests were performed for continuous variables, and Chi-square or Fisher's exact tests were performed for categorical variables. A two-sided p value<0.05 was considered to be statistically significant.

Results

A total of 1,019 patients underwent LNF for GERD as inpatients between 2005 and 2008 in North Carolina. LNF for GERD was more common than open fundoplication as the percentage of LNF averaged 86.2% over a 4-year period (Fig. 1). The North Carolina inpatient database includes 62 hospitals. Nine hospitals (14%) were identified as high-volume centers as defined by averaging at least ten LNF per year between 2005 and 2008. High-volume centers performed 530 LNFs (52%) while low-volume centers performed 489 LNFs (48%) (Fig. 2). Overall median age was 51 years, and median length of stay was 2 days. The most prevalent pre-operative comorbidities among all patients from both high- and low-volume centers included the presence of a hiatal hernia (52.2%), hypertension (32.7%), tobacco abuse (16.6%), asthma (15.4%), and diabetes (11.1%). The most common complications included atelectasis (3.9%), accidental puncture or laceration (2.1%), and respiratory complications (1.9%). Patients at high-volume centers were older (median 52.5 years old vs. 49.0 years old, p=0.019) (Fig. 3), had a higher incidence of diabetes (13.4% vs. 8.8%, p=0.026), chronic obstructive pulmonary disease (5.1% vs. 2%, p=0.015), hyperlipidemia (9.6% vs. 4.7%, p=0.004), and cystic fibrosis (2.8% vs. 0.8%, p=0.03) (Table 1). There were no deaths among the two groups and also no difference between gender and median length of stay (2.7 days for high-volume center vs. 2.6 days for low-volume center). Patients with a history of transplantation

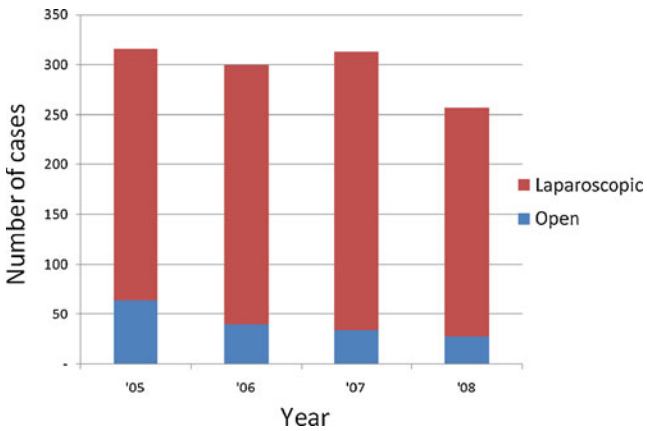

Fig. 1 Laparoscopic vs. open fundoplication for GERD between 2005 and 2008

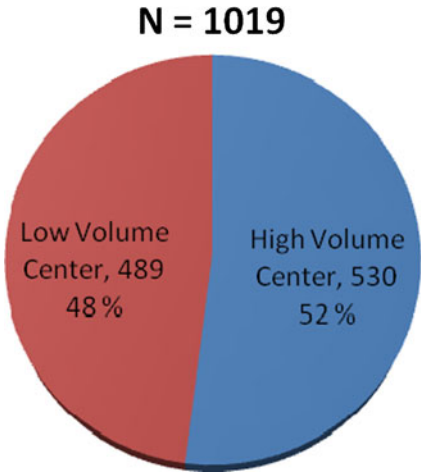

Fig. 2 Number of LNF performed by low-volume vs. high-volume centers

were also more likely to undergo LNF at a high-volume center (15.8% vs. 1.6%, p<0.0001) Low-volume centers had a higher incidence of intraoperative accidental puncture or laceration (3.3% vs. 0.9%, p=0.017), while high-volume centers had a higher incidence of atelectasis (5.3% vs 2.5%, p=0.031) (Table 2).

Discussion

As expected, LNF has virtually replaced the open surgical alternative for the treatment of GERD in North Carolina. LNF is an accepted treatment for GERD with patient satisfaction and safety demonstrated by peer review data.[2–4,19] Nationally, the number of antireflux procedures as well as the percentage done laparoscopically has also increased considerably.[1,6,20] However, there are several findings in this study that are intriguing and warrant careful examination. First, there is a large proportion of LNFs being done at low-volume centers by surgeons that perform this operation only a few times per year. Second, the rate of accidental perforation is higher at low-volume centers. Third, we found no difference in mortality or hospital LOS, despite the higher

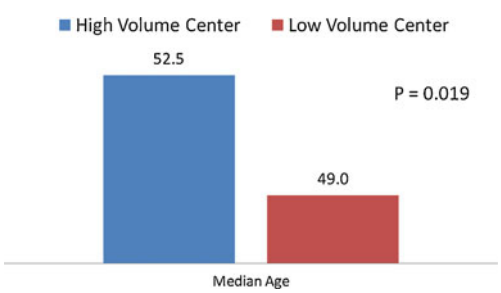

Fig. 3 Comparison of median age between high- and low-volume centers

Table 1 Comparison of comorbidities between high-volume and low-volume centers

Comorbidities	High volume		Low volume		*p* value
	Total	Percentage	Total	Percentage	
Barrett's esophagus	41	7.70	27	5.50	NS
Hiatal hernia	284	53.60	248	50.70	NS
Esophageal stricture	6	1.10	13	2.70	NS
Esophageal dyskinesia	5	0.90	13	2.70	NS
Obesity	53	10.00	37	7.60	NS
CAD/atherosclerosis	29	5.50	27	5.50	NS
MI	8	1.50	1	0.20	NS
Diabetes	71	13.40	43	8.80	0.026
Hypertension	169	31.90	164	33.50	NS
Chronic kidney disease	15	2.80	5	1.00	NS
COPD	27	5.10	10	2.00	0.015
CNS	18	3.40	28	5.70	NS
Tobacco abuse	81	15.30	88	18.00	NS
Vascular disease	3	0.60	5	1.00	NS
Asthma	74	14.00	83	17.00	NS
Arrhythmia	17	3.20	21	4.30	NS
Adhesions	52	9.80	46	9.40	NS
Gastroparesis	5	0.90	12	2.50	NS
Transplant	84	15.80	8	1.60	<0.001
Hyperlipidemia	51	9.60	23	4.70	0.004
Cystic fibrosis	15	2.80	4	0.80	0.033
Obstructive sleep apnea	28	5.30	22	4.50	NS
Neoplasm	28	5.30	25	5.10	NS

CAD coronary artery disease, *MI* myocardial infarction, *CNS* central nervous system, *COPD* chronic obstructive pulmonary disease, *NS* not significant with $p>0.05$

perforation rate in the low-volume centers. Prior to making comments or general recommendations with respect to the application of this data, we feel that it is essential to understand the strengths and weaknesses of our data and how it may be interpreted.

Limitations of our study include the use of administrative data in the inpatient setting only. We were unable to obtain similar data in the outpatient setting as hospital-specific data was not available and without being able to categorize hospitals into high-and low-volume centers, they could not be compared in the same fashion as the inpatient dataset. This leads to a significant problem in that there is a large number of LNFs that are likely performed in the outpatient or day-case setting (i.e., 23-h stay). The rapid recovery of LNF as compared to open antireflux surgery has no doubt popularized an outpatient approach. In a review of seven articles with over 900 cases of LNF being performed on a day-case basis, the average discharge time ranged from 2 h and 25 min to 24 h.[21] In fact, our own institution could not be studied because patients undergoing LNF were admitted as a day-case (23-h stay) as opposed to an inpatient. As such, our results were not captured by the state-wide inpatient database. One could also surmise that inpatient admissions would only be those faced with complications that would require a longer hospital stay. With improvements in surgical therapies requiring only outpatient or day-case hospital stays, more advanced tracking tools will be necessary to measure results from different institutions. Despite this weakness, we feel that the large volume of cases reported without the influence of the operating surgeon lends itself a unique perspective through which LNF has not been previously studied. Moreover, prior to 2005, there was no specific ICD-9 code for LNF, and efforts to track outcomes with population-based databases have been accomplished largely by inference and assumption. For example, Finlayson and Finks estimated the number of laparoscopic antireflux operations from 1997 to 2003 by identifying specific discharges involving fundoplication that also included a code for laparoscopic exploration, laparoscopic lysis of adhesions, or laparoscopic cholecystectomy or were associated with a live discharge with a length of stay$\leq$2.[1,22] In contrast, we were able to use the specific ICD-9 code for LNF (44.67) to accurately query our state-wide inpatient database, which ultimately revealed that almost half of the LNF were being performed at low-volume centers. This represents 489 cases during the study period. If this is the case, there is no literature to support such a practice pattern of which the results are unknown or

Table 2 Comparison of complications between high-volume and low-volume centers

Complications	High volume		Low volume		*p* value
	Total	Percentage	Total	Percentage	
Wound hematoma	1	0.20	1	0.20	NS
Seroma	0	0.00	0	0.00	NS
Abscess	2	0.40	1	0.20	NS
PE	3	0.60	1	0.20	NS
Sepsis	0	0.00	2	0.40	NS
DVT	0	0.00	0	0.00	NS
Aspiration	0	0.00	0	0.00	NS
Respiratory complications	13	2.50	6	1.20	NS
Cardiac complications	4	0.80	3	0.60	NS
Digestive system complication	8	1.50	15	3.10	NS
Central nervous system complication	1	0.20	0	0.00	NS
Urinary complication	6	1.10	1	0.20	NS
Iatrogenic pneumothorax	2	0.40	0	0.00	NS
Accidental laceration	5	0.90	16	3.30	0.017
Atelectasis	28	5.30	12	2.50	0.031
Transfusion of RBCs	2	0.40	5	1.00	NS
Respiratory arrest	1	0.20	1	0.20	NS
Hemorrhage	4	0.80	5	1.00	NS
Post-operative infection	2	0.40	3	0.60	NS
Other specified complication	4	0.80	4	0.80	NS
Death	0	0.00	0	0.00	NS

PE pulmonary embolism, *DVT* deep venous thrombosis, *NS* not significant with $p>0.05$

unreported. Thus, informed consent under such circumstances should reflect the institution and surgeons experience and not rely on data from high-volume centers to help patients in their treatment decisions.

Another limitation of our study is that we could not track readmission rates or reoperations specific to select patients because database information is deidentified. Reoperative rates from prospective series' range from 1.2% to 17%.[2,4,7,9,23,24] In these series, patients requiring reoperation either incurred a complication from primary LNF such as bleeding or perforation or had symptoms related to a technical failure such as a slipped, twisted, or herniated wrap.[9] Gee et al. also demonstrated that patients undergoing redo laparoscopic fundoplication had higher gastroesophageal reflux disease-health-related quality-of-life scale (GERD-HRQL), lower satisfaction, and a greater probability of requiring antireflux medication.[7] Since results from redo laparoscopic antireflux operations are not as good, reoperations not only represent failed primary LNF but also a risk factor for future redo LNF. Our data cannot elucidate whether LNF were performed primarily or as a redo operation nor can it track the hospitalization of the patients incurring a complication. However, despite having three times more accidental punctures or lacerations, patients from low-volume centers had no difference in hospital length of stay and no mortality. This suggests that either the puncture was of no consequence or more likely, the patient was transferred to tertiary care center for further evaluation and care.

In many cases, complications and failures from laparoscopic antireflux surgery have been attributed to operative technique.[6–12,17,23] It is evident that LNF has a learning curve.[3,12] The rate of revisional operations has been observed to decrease when examining a series of cases in chronological order.[4] Thus, it is logical to infer that more experienced surgeons would have less procedural failures and complications. Interestingly, Carlson and Frantzides reviewed over 10,000 minimally invasive antireflux operations and still maintained that their data was not appropriate to compare "experts" versus "nonexperts".[6] Thus, this issue begs further investigation as it plays a major role in the discrepancies that arise in this study and other studies like it.

One way to make the distinction between expert and non-expert is to compare teaching hospitals with community hospitals. Morton et al.[20] did this by comparing the Nationwide Inpatient Sample (NIS) to the SAGES Outcome Project for all fundoplications (open and laparoscopic) between 1999 and 2001. They found that the percentage of cases being performed at teaching hospitals was significantly higher in the SAGES Outcomes Project database and concluded that despite having more comorbidities and

technical difficulties, patients from the SAGES Outcomes Project database had equivalent or lower complication rates, suggesting that surgeons associated with teaching hospitals had better outcomes. This is not an uncommon referral pattern as complex patients benefit from the multitude of services offered at larger teaching hospitals. Our data also revealed that high-volume centers perform LNF on significantly older patients with more comorbidities with equivalent results. Interestingly, our data also revealed that that only 24% of LNF were performed at teaching hospitals. Moreover, of the nine centers considered to be high volume, only three were also teaching hospitals. This discrepancy may be explained by an increase in outpatient or day-case LNF performed at teaching hospitals, as demonstrated by our own institution or by the dissemination of LNF in the community setting. The latter is reinforced by Finks et al.,[22] who found that although the percentage of LNF remained the same between 1999 and 2003 (69% in 1999 vs. 68% in 2003, $p=0.548$), there was a significant decrease in the number of procedures being performed at teaching hospitals (53% in 1999 vs. 48% in 2003, $p<0.0001$), suggesting that LNF was being more widely performed in community or private hospitals. Should this be the case, it appears as though complex surgeries are not uniformly referred to teaching hospitals or high-volume institutions.

The impact of hospital volume on surgical mortality has been well documented for a variety of complex surgical procedures.[25–29] Data from these large population-based studies have also provided the impetus for realizing the benefits of volume standards and regionalization.[27] In a study that analyzed 2.5 million procedures, Birkmeyer et al., [28] demonstrated that mortality decreased as hospital volume increased for all of the 14 types of procedures examined, which ranged from cardiovascular procedures to a multitude of abdominal surgeries (i.e., esophagectomy, gastrectomy, pneumonectomy, cystectomy, and pancreatectomy). Moreover, the most dramatic differences in mortality were found between very-low-volume and very-high-volume hospitals for pancreatic resection and esophagectomy, which were among the least common procedures overall and also among the more complex. Birkmeyer et al.[26] goes on to argue that if volume standards are successfully implemented, employers and health-care purchasers could prevent many surgical deaths by requiring hospital volume standards for high-risk procedures.

When analyzing data for LNF, it is apparent that two main issues need to be resolved. First, in-hospital mortality is not an applicable indicator, since there were no reported deaths in either the high- or low-volume centers. Thus, reported data on LNF as well as other minimally invasive procedures must also include readmissions, reoperations, and transfers to another facility in both the inpatient and outpatient setting. In doing so, one would be able to more clearly demonstrate an effect in the utility of regionalization for minimally invasive procedures as poorer outcomes would tend to result in an increase in hospital care, resources, and spending. Second, how many LNF are necessary to be considered a high-volume center? Our study demonstrates that doing less than ten LNF per year results in a significantly higher incidence of accidental perforations. Although the idea of a learning curve for LNF has been studied, maintenance of skill has not been studied. Once a surgery is learned, how many cases per year are required to keep one's skills and decision-making at peak performance? The answer to this question is not unique to minimally invasive surgery as technique and technology are evolving in all aspects of surgery. Thus, this issue begs further development of tools that are designed for lifelong surveillance after operative procedures. A mandatory data base for all operations that utilizes unique patient identifiers can be used for both short-term and long-term data analysis. Such a database can also objectively measure medical encounters without relying on conventional self reporting. Until such a system is in place, making general guidelines for the application of surgical procedures to large patient populations will only be as good as the data is.

Conclusion

A significant proportion of the LNFs in North Carolina are performed at low-volume centers. High-volume centers perform LNF on older patients with more comorbidities. Low-volume centers have three times more accidental perforations. Yet there is no detectable difference in mortality or median length of stay. It is impossible to tell if these perforations are managed at these low-volume centers or transferred to facilities with a higher level of care. These findings argue for regionalization of LNF and for a reevaluation of the global safety of this operation.

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2010 SSAT PLENARY PRESENTATION

Pay for Obesity? Pay-for-Performance Metrics Neglect Increased Complication Rates and Cost for Obese Patients

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Abstract
Background Rates of surgical complications are increasingly being used for pay-for-performance reimbursement structures. We hypothesize that morbid obesity has a significant effect on complication rates and costs following commonly performed general surgical procedures.
Methods We studied 30,502 patients who underwent cholecystectomy for cholecystitis and 6,390 patients who underwent appendectomy for acute appendicitis using administrative claims data from seven Blue Cross and Blue Shield Plans over a 7-year period (2002–2008). We compared 30-day complications as well as total 30-day direct medical costs for obese and non-obese patients. Multivariate regressions were performed to determine the relationship of morbid obesity to complications and cost.
Results Obese patients were more likely to have a complication within 30 days after surgery than non-obese patients (19.2% vs. 15.7% for cholecystectomy, $p<0.0001$; 20.2% vs. 15.2%, $p<0.0001$, for appendectomy). The mean total 30-day postoperative cost for obese patients were $1,109 higher following a cholecystectomy ($p<0.0001$) and $666 higher following an appendectomy ($p=0.09$).
Conclusion Morbid obesity is associated with a higher rate of complications for two commonly performed general surgical procedures and is associated with higher costs for cholecystectomy. Pay-for-performance metrics should account for the increased risk of complications and higher cost in this population.

Keywords Obesity · Appendectomy · Cholecystectomy · Pay for performance · Cost

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Introduction

Pay-for-performance (P4P) initiatives that use surgical complication rates to determine compensation are being widely adopted among federal, state, and private sector health care payers.[1–4] Increasingly, hospitals and health care providers are given financial incentives to optimize processes of care and outcomes. However, there has been growing frustration in the medical and surgical community that such outcome metrics ignore intrinsic differences in complication rates associated with patient comorbidities known to impact outcomes. Obesity is one of the fastest growing and most prevalent major comorbidities that surgeons encounter. Previous studies have suggested its influence on outcomes after general surgery procedures.[5–8]

Since its introduction, providers have been concerned that pay-for-performance compensation plans do not appropriately reimburse for the added work and costs associated with high-risk cases; however, these added risks and costs have not been well-defined. To address this question, we designed a study to measure the risk of complications and cost of obese patients who undergo two commonly performed acute general surgery operations—appendectomy for acute appendicitis and cholecystectomy for acute cholecystitis.

Methods

Our dataset included administrative claims data from 2002 to 2008 for over 3.8 million insured lives from seven Blue Cross and Blue Shield health plans (Blue Cross and Blue Shield Association, Blue Cross and Blue Shield of Tennessee, Blue Cross and Blue Shield of Hawaii, Blue Cross and Blue Shield of Michigan, Blue Cross and Blue Shield of North Carolina, Highmark Inc. of Pennsylvania, Independence Blue Cross of Pennsylvania, Wellmark Blue Cross and Blue Shield of Iowa, and Wellmark Blue Cross and Blue Shield of South Dakota). These data were made available as part of a collaborative effort between Johns Hopkins University and Blue Cross and Blue Shield Plans studying the effects of obesity on health outcomes and cost. The overall composition of the dataset was originally constructed to develop a claims-based risk score to identify obese patients and is described previously.[9]

Within this dataset, we examined all patients between the ages of 18 and 64 who submitted claims for cholecystectomy for acute cholecystitis or appendectomy for acute appendicitis. Patients aged 65 and over were excluded because these patients' costs are confounded by the use of Medicare. Obesity was identified by (1) body mass index (BMI) >35 in those patients who completed a health risk assessment questionnaire or (2) had a claim containing a diagnosis of obesity. Thirty-day postoperative events were identified from the claims data, including length of stay, readmission within 30 days after operation, death, cardiovascular event, venous thromboembolic event, reoperation, GI complications, infectious complications, hemorrhage, respiratory complication, and genitourinary complication. The data used for this study were de-identified in accordance with the Health Insurance Portability and Accountability Act of 1996 definition of a limited dataset and were used in accordance with federal standards for protecting confidentiality of the personal health information of the enrollee.

All costs associated with the acute hospitalization and within 30 days post-procedure were calculated from claims data. Physician payments were standardized by current procedural terminology (CPT) code. If a claim had a missing or nonpositive payment amount after the above procedure was followed, then the payment was imputed from the claims with non-missing payments, based on the insurance plan, code (DRG, CPT, or ICD procedure code), and year. For the purposes of this study, cost represents the amount paid by each health insurance plan for a given claim.

For the univariate analysis, the chi-square test was used for the categorical values, and the t test was used for continuous variables. Mean log-transformed costs were used to compare obese and non-obese cohorts within each procedure category. For the multivariate analysis, a logistic regression was used to model the development of any complication, and an ordinary least squares regression on log-transformed costs was used to model the effects on costs.

Results

A total of 6,390 patients (1,082 obese and 5,308 non-obese patients) were identified who underwent appendectomy for acute appendicitis, and 30,502 patients (4,678 obese and 25,824 non-obese patients) underwent cholecystectomy for acute cholecystitis. Patient characteristics are described in Table 1. Obese patients who underwent appendectomy had higher rates of diabetes and sleep apnea (Table 1). Obese patients who underwent cholecystectomy had a higher rate of diabetes, hypertension, and sleep apnea (Table 1). The obese patients in both groups were younger and included more women.

Thirty-day postoperative outcomes are outlined in Table 2 for both the appendectomy and the cholecystectomy groups. The mean length of stay was slightly longer for the obese as compared to non-obese patients undergoing both procedures. The difference was statistically significant for obese patients undergoing appendectomies. The overall complication rate as defined by the occurrence of at least one of the listed categories were higher in obese patients undergoing appendectomy and cholecystectomy (20.2% vs. 15.3%, $p<0.0001$ and 19.2% vs. 15.7%, $p<0.0001$, respectively) as compared to non-obese patients. Obesity did not affect 30-day mortality after either procedure. In examining specific categories of complications, the greatest difference between obese and non-obese patients was seen in the rate of infectious complications (appendectomy, 9.0% [obese patients] vs. 5.0% [non-obese patients] and cholecystectomy, 3.7% [obese patients] vs. 2.1% [non-obese patients]). This likely reflects the higher rate of surgical site infections noted in the obese cohort. Obese patients undergoing either appendectomy or cholecystectomy were also at a significantly increased risk of respiratory complications and reoperation during the hospital stay.

Table 1 Patient characteristics

	Obese, *N*=1,082	Non-obese, *N*=5,308	*p* value
Appendectomy			
Mean age (SE)	43.5 (0.4)	47.3 (0.2)[b]	<0.001
Female (%)	597 (55.2)	2,400 (45.2)[b]	<0.001
Laparoscopic (%)	474 (43.8)	2,441 (46.0)[b]	0.019
Diabetes (%)	223 (20.6)	802 (15.1)[b]	<0.001
Hypertension (%)	404 (37.3)	1,819 (34.3)[b]	0.053
Sleep apnea (%)	113 (10.4)	240 (3.6)[b]	<0.001
Cholecystectomy			
	Obese, *N*=4,678	Non-obese, *N*=25,824	*p* value
Mean age (SE)	44.8 (0.2)	46.1 (0.1)	<0.001
Female (%)	3,502 (74.9)	17,374 (67.3)	<0.001
Laparoscopic (%)	4,398 (94.0)	24,265 (94.0)	0.892
Diabetes (%)	1,032 (22.1)	2,896 (11.2)	<0.001
Hypertension (%)	2,001 (42.8)	7,465 (28.9)	<0.001
Sleep apnea (%)	403 (8.6)	576 (2.2)[d]	<0.001

[a] *N* = 1,082
[b] *N* = 5,308
[c] *N* = 4,678
[d] *N* = 25,824

Table 2 Thirty-day postoperative outcomes following procedures

	Obese, *N*=1,082	Non-obese, *N*=5,308	*p* value
Appendectomy			
Any complication, *n* (%)	219 (20.2)	813 (15.3)	<0.001
Readmission within 30 days	72 (6.7)	278 (5.2)	0.062
Death	1 (0.1)	1 (0.02)	0.310
Cardiovascular	44 (4.1)	207 (3.9)	0.797
Thromboembolic event	12 (1.1)	36 (0.7)	0.135
Reoperation	22 (2.0)	46 (0.9)	0.001
GI complication	67 (6.2)	240 (4.5)	0.019
Infectious complication	97 (9.0)	268 (5.0)	< 0.001
Hemorrhage	20 (1.8)	38 (0.7)	<0.001
Respiratory complication	42 (3.9)	143 (2.7)	0.034
Genitourinary complication	35 (3.2)	152 (2.9)	0.509
Mean length of stay (SE)[a]	4.3 (0.2)	4.0 (0.05)[b]	0.040
Cholecystectomy			
Outcome	Obese, *N*=4,678	Non-obese, *N*=25,824	*p* value
Any complication, *n* (%)	900 (19.2)	4,064 (15.7)	<0.001
Readmission within 30 days	305 (6.5)	1,528 (5.9)	0.110
Death	8 (0.2)	49 (0.2)	0.785
Cardiovascular event	255 (5.5)	1,136 (4.4)	0.002
Thromboembolic event	53 (1.1)	219 (0.8)	0.056
Reoperation	52 (1.1)	149 (0.6)	<0.001
GI complication	306 (6.5)	1,519 (5.9)	0.080
Infectious complication	173 (3.7)	537 (2.1)	<0.001
Hemorrhage	58 (1.2)	276 (1.1)	0.301
Respiratory complication	180 (3.8)	798 (3.1)	0.007
Genitourinary complication	143 (3.1)	685 (2.7)	0.117
Mean length of stay (SE)[a]	4.8 (0.1)	4.6 (0.04)	0.059

[a] A *t* test was used for the means; a chi-square test was used for all other comparisons

Inpatient costs were calculated for the hospitalization associated with the index operation. Additional claims, excluding pharmacy, submitted within a 30-day period after the operation were also identified and included in the total cost calculations. The mean costs are tabulated in Table 3. On a univariate analysis, the obese patients incurred significantly higher costs than non-obese patients for cholecystectomy (p <0.001). In the appendectomy group, there was a trend towards higher overall costs in the obese group, but not statistically significant (p=0.091). Payments were $666 higher in obese patients following appendectomy and were $1,109 higher in obese patients following cholecystectomy.

A multivariate logistic regression was performed to model the odds of experiencing a complication. These results are summarized in Table 4. On a multivariate analysis, the obese patients had a relative risk of 1.43 (confidence interval (CI), 1.21–1.70) for developing a complication after appendectomy and 1.19 (CI, 1.09–1.29) for developing a complication after cholecystectomy. Obesity was associated with a statistically significant increased cost in the cholecystectomy group on the multivariate analysis, after controlling for the comorbidities that were unequally distributed between the obese and non-obese groups (diabetes, hypertension, sleep apnea), as well as age (p<0.001).

Discussion

P4P initiatives have been heralded as a success in introducing financial performance incentives into medicine with the goal of improving quality of care and reducing health care expenditures. With rapidly exploding popularity, they have been adopted at the federal, state, and hospital level to financially reward good provider outcomes and punish poor performance.[1–4] However, despite the conceptual appeal of P4P policies, those that are based on outcome measures require risk adjustment, otherwise, providers who care for higher risk patients would be unfairly penalized.[10,11] We believe that obesity is an important comorbidity that must be included when defining high-risk populations because of its effect on perioperative outcomes, its rapidly increasing prevalence in the United States, and its unequal distribution geographically, racially, and socioeconomically.[12] The goal of this study was to identify if a diagnosis of morbid obesity correlated with higher rates of postoperative morbidity, mortality, and cost after two acute general surgery procedures: appendectomy and cholecystectomy. We focused on these procedures because they are commonly performed with a standard approach to management and the majority of costs stemming from the procedure occur within 30 days of the procedure.

Our findings suggest that morbidly obese patients have increased complication rates following appendectomy for acute appendicitis and cholecystectomy for acute cholecystitis. Much of the excess morbidity observed in the obese patients was infectious in nature, predominantly surgical site infections. Previous data regarding morbidity and mortality following general surgical procedures in the obese are mixed.[5–8,13,14] Many groups have reported that obese patients have an increased rate of surgical site infection, especially in patients with very high BMI (>40). Mortality and other complication rates have not been clearly shown to be higher in obese patients, and in fact an "obesity paradox" has been suggested by some studies,[8] indicating improved outcomes in obese patients. However, our study is not necessarily incongruous with these previous findings. First, we selected only acutely ill patients, namely those with acute appendicitis or acute cholecystitis who required urgent or emergent operations. Thus, the acute nature of the procedures we studied may be amplifying the effect of obesity on perioperative complications. Obese patients may have delayed presentations for acute appendicitis and cholecystitis and thus have more severe disease at the time of operation. Second, since we only selected acute procedures, the treating physician's ability to optimize comorbidities preoperatively is limited. Both of these aspects of acute care surgery may influence the effect of obesity on postoperative outcomes.

Our study also demonstrates a statistically significant increased cost of care for obese patients undergoing cholecystectomy and a trend towards increased cost for obese patients undergoing appendectomy. On average,

Table 3 Unadjusted costs for surgical admission and 30-day follow-up

	Obese	Non-obese	p value[a]
Appendectomy			
Inpatient cost	$13,995 (12,604–15,387)	$13,872 (12,847–14,898)	0.142
Post-discharge	$2,371 (1,410–3,331)	$1,828 (1,468–2,188)	<0.001
Total 30-day cost	$16,366 (14,607–18,125)	$15,700 (14,589–16,811)	0.091
Cholecystectomy			
Inpatient cost	$17,296 (15,770–18,822)	$15,942 (15,427–16,456)	<0.001
Post-discharge	$2,440 (1,933–2,948)	$2,685 (2,404–2,966)	<0.001
Total 30-day cost	$19,736 (18,101–21,372)	$18,627 (18,006–19,247)	<0.001

[a] t test of log-transformed costs in dollars

Table 4 Multivariate regression for development of any complication and overall cost

	Any complication			Cost				
	Likelihood ratio	95% confidence interval	*p* value	Cost: regression coefficient	95% conf interval	Cost (percent change)	95% confidence interval	*p* value
Appendectomy								
Obesity	1.43	1.21–1.70	<0.001	1,334.1	−12.6–2,793.9	8.4	−0.1–17.6	0.052
Laparoscopic (vs. open)	0.90	0.79–1.03	0.142	2,132.3	1,078.8–3,251.5	13.4	6.8–20.5	<0.001
Age								
35–44	1.14	0.90–1.46	0.278	1,987.6	317.8–3,828.2	12.5	2.0–24.2	0.018
45–54	1.34	1.07–1.68	0.012	2,318.1	703.0–4,089.2	14.6	4.5–25.9	0.004
55–64	1.82	1.45–2.28	<0.001	5,579.3	3,613.3–7,741.8	35.2	22.9–48.9	<0.001
Male	1.05	0.91–1.20	0.498	206.9	−738.1–1,209.4	1.3	−4.6–7.6	0.676
Diabetes	1.25	1.05–1.49	0.014	3,458.6	1,891.7–5,164.1	21.8	12.0–32.7	<0.001
Hypertension	1.21	1.04–1.40	0.013	1,109.3	0.00–2,296.4	7.0	0.00–14.5	0.050
Sleep apnea	1.48	1.14–1.93	0.003	3,506.8	1,109.3–6,244.1	22.1	7.0–39.5	0.003
Cholecystectomy								
Obesity	1.19	1.09–1.29	<0.001	1,598.15	946.0–2,269.8	8.5	5.0–12.1	<0.001
Laparoscopic (vs. open)	0.52	0.46–0.58	<0.001	−8,036.34	−8,542.7 to −7,505.0	−42.8	−45.5 to −39.9	<0.001
Age								
35–44	1.12	1.01–1.25	0.038	632.59	−43.2–1,332.7	3.4	−0.2–7.1	0.067
45–54	1.30	1.17–1.44	<0.001	1,029.06	362.5–1,720.9	5.5	1.9–9.2	0.002
55–64	1.79	1.61–1.98	<0.001	3,164.64	2,402.9–3,956.0	16.8	12.8–21.1	<0.001
Male sex	1.28	1.20–1.36	<0.001	2,375.38	1,846.4–2,915.7	12.6	9.8–15.5	<0.001
Diabetes	1.50	1.38–1.63	<0.001	3,876.51	3,070.4–4,712.3	20.6	16.3–25.1	<0.001
Hypertension	1.39	1.29–1.49	<0.001	2,549.70	1,974.8–3,138.3	13.6	10.5–16.7	<0.001
Sleep apnea	1.51	1.30–1.75	<0.001	1,342.79	60.3–2,712.6	7.1	0.3–14.4	0.040

payments associated with the inpatient hospitalization and 30 days postoperatively averaged $1,109 higher in obese patients undergoing cholecystectomy and $666 higher when undergoing appendectomy. This effect of obesity on costs was significant in the multivariate analysis for the cholecystectomy group. Although many factors likely explain why costs were higher in the obese group, we believe that this effect is driven by the higher rate of postoperative complications intrinsic to this population. Other possibilities to explain this difference include differences in severities of illness, ASA classification, and the presence of other diagnoses not captured in the claims dataset we used. Furthermore, one could hypothesize that obese patients consume more inpatient health care resources even without the presence of a significant complication; for example, more radiographic studies or laboratory tests may be required in obese patients. Our dataset is unable to distinguish among these different possibilities, but there does appear to be a significant independent impact of obesity on the amounts paid by the health care plans included in the dataset. If non-risk-adjusted P4P incentives were to be implemented in this patient population (for example, based on surgical site infection rates), the reimbursement rates would reverse, penalizing those who care for higher numbers of obese patients. Providers would not only be paid the same standard reimbursement for obese patients as they are paid for lower-risk non-obese patients, but they would actually be penalized by pay-for-performance policies for the occurrence of complications in obese patients. Furthermore, as obesity has a higher prevalence in the minority and the lower income populations, many hospitals that disproportionately care for these high-risk patients are being penalized by unadjusted P4P policies.

This study has several important limitations because it was conducted using an insurance claims database. First, the identification of a postoperative complication is dependent on a claim being accurately recorded in the dataset using the correct diagnosis and code. Although this method of identifying surgical complications is not as sensitive as the review of each patient's medical record or prospective data collection, the rates of complications that we identified are comparable to prior studies. Further, the method of detecting events based on codes was the same in each comparison group. Second, our ability to determine a patient's obesity status was similarly limited. We defined obese and non-obese patients based on the presence of an obesity diagnosis code or body mass index information through health risk assessment questionnaires. This likely underestimates the number of obese patients in the dataset, as some patients who do not carry a diagnosis of obesity or have BMI information available may still be obese, whereas those who do carry a diagnosis of obesity are unlikely to be non-obese.

Because of the way in which the dataset was originally constructed,[9] the appendectomy cohort did not include all patients who underwent appendectomy operations, but instead only patients who underwent an appendectomy and had one of the original dataset inclusion criteria (a diagnosis of obesity, an obesity-related comorbidity, or completion of a health risk assessment). Therefore, the appendectomy group overall is enriched with obese patients compared to the population at large. Consequently, our results probably underestimate the true impact of obesity on outcomes and cost (type II error) since our non-obese cohort is likely contaminated with many obese patients. This did not apply to the cholecystectomy group as all patients who underwent cholecystectomy were included in the original dataset. Another limitation is our definition of cost as payments made by the various health insurance plans included in the dataset. This definition does not include costs that are shouldered by the hospital, the provider, or the patient. Although paid reimbursements represent one measurement of cost, an overall societal perspective would provide a broader view of the costs of surgical care but would be beyond the scope of this paper.

There are several important policy implications from our study. First, structure and process measures may be incentivized, but outcome measures should only be used in P4P models when they are risk-adjusted. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) is one such validated risk-adjusted means of benchmarking outcomes at a hospital level. We warn that failure to risk-adjust could lead to the discrimination against high-risk populations and penalize doctors and hospitals who disproportionately care for these patients. Many doctors have already raised the issue of P4P policies to highlight disparities of care.[15,16] Our study suggests that obese patients are at increased risk of complications following two acute general surgery procedures, appendectomy and cholecystectomy, and incur higher costs for these procedures. Payers should consider reimbursing operations on obese patients with a cost adjustment that accounts for the additional complications that obese patients experience after surgery. Our results also begin to frame the financial impact of obesity on the health care system. We propose that obesity be included in any risk-adjustment strategy for appropriate P4P compensation.

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Discussion

Dr. David McFadden (Burlington, VT): Primary discussants have been given 1 min, so congratulations on a very important topic, a great manuscript, and an outstanding presentation.

I'll just ask a couple of questions because I know there are a lot of people in the audience who want to comment on this very provocative paper.

As you mentioned, there is a cost–charge payment continuum. Your findings of increased payments intuitively represents increased charges and increased costs. Do you think the incremental payment offsets the incremental real cost to the health care providers? If not, and given the already narrow margins on these two conditions, care may indeed become a losing proposition for these obese patients, especially those without commercial insurance.

Secondly, although the length of stay did not differ between the groups, it does appear a little excessive, especially in a Blue Cross population. You had a 5-day length of stay for cholecystectomy and a 4-day length of stay for appendectomy. I am just interested in your thoughts or comments about this.

Closing Discussant

Dr. Kenzo Hirose: Cost obviously is a very difficult topic to analyze, and certainly it depends on one's perspective. The perspective of this paper is from the health care payer. And in some sense, the motivation is to reduce costs as much as possible. And that means basically reducing the amount that is reimbursed to either the provider or the hospital.

And again, in terms of the burden to the provider and the hospital of caring for these patients, certainly this doesn't address any of those costs inherent in caring for these patients. And doing so would take a different analytic approach.

The way we looked at it, it certainly has a number of caveats and depends on various reimbursement modes, fee-for-service versus others, and certain contracts that each of the healthcare payers has with their associated hospitals and providers. So with those caveats, this is how we looked at costs because we had access to these numbers. It certainly doesn't address a lot of the other questions regarding whether it's a losing proposition to take charge of these patients or not. It's certainly an important question to ask.

In terms of the length-of-stay numbers, for I believe, in terms of cholecystectomy, our mean hospital stay was 4 or 5 days. We did notice that this was fairly long. I believe we selected for patients that had somewhat more severe disease. These were patients who underwent urgent or emergent operations with acute inpatient hospitalization. It is not necessarily postoperative length of stay either, and it would include any stay prior to their surgery. So we believe that we have selected for a group of patients that may have a little bit more severe disease.

Discussant

Dr. Henry Pitt (Indianapolis, IN): Very nice work. We've been looking at pancreatectomy, a high-risk operation, in conjunction with the statisticians at the American College of Surgeons National Surgical Quality Improvement Program. We and found, like you did, that obesity is a risk factor for mortality, serious morbidity, and overall morbidity for this high-risk operation. In the NSQIP database, they have five categories of obesity, and somewhat to my surprise, only BMI greater than 40 was the factor that increased the risk for pancreatectomy.

You had just two categories, less than and more than BMI of 35. Do you think the cutoff, if you had better data, would be higher than 35?

Closing Discussant

Dr. Kenzo Hirose: Part of our data is based on the BMI, but also a large portion of patients were ones that carried a diagnosis of obesity. So this is one of the sorts of the risks of using administrative claims data to look at these patients. Some of these patients needed to carry a diagnosis of obesity, so this probably skewed the population to patients who had more severe forms of obesity. So someone who has a BMI of greater than 35, who doesn't have comorbidities, probably would not be carrying the diagnosis of obesity. There's a bit of a coding bias that is inherent in the way we looked at our patients. We recognized this, although we felt that in terms of the bias, that this would probably bias patients in the obese group to be of higher BMIs and have higher comorbidities and potentially have contaminated our non-obese group with a certain number of obese patients. But we felt that this type of bias would have, if anything, reduced the effect that we were looking for. Thus, we feel that the effect that we see is legitimate one.

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ORIGINAL ARTICLE

Comparison of a Novel Technique of the Microlaparoscopic Pyloromyotomy to Circumbilical and Weber–Ramstedt Approaches

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Abstract
Introduction The aim of this retrospective comparative study was to compare the surgical results and outcomes of the newly inaugurated approach of microlaparoscopic pyloromyotomy with open techniques.
Methods The surgical charts of 110 infants (85 boys and 25 girls, ages ranging from 10 to 98 (average 28) days) undergoing pyloromyotomy microlaparoscopically (28), through the circumbilical approach (56), or via the right upper quadrant access (26) were reviewed. The variables were compared between the three surgical approach groups, and the statistical analysis was performed.
Results There was a significant difference between Bianchi and microlaparoscopy in terms of operation time (average 38.5 vs. 20.5 min, $p<0.0001$) and time to full enteral feed (average 48 vs. 32 h, $p=0.001$). There was no significant difference in postoperative length of stay (75 vs. 82 h, $p=0.12$). The operative time for the surgeons experienced in microlaparoscopy was in average of 14 min (range, from 9 to 18 min). When comparing the Weber–Ramstedt procedure and microlaparoscopy, microlaparoscopy required significantly less operative time (50 vs. 20 min, $p<0.0001$), a shorter time to full enteral feed (70 vs. 32 h, $p<0.001$), and a shorter postoperative length of stay (90 vs. 82 h, $p=0.04$). There were no cases of mucosal perforation or incomplete pyloromyotomy.
Conclusion Despite the small sample size included in the present study, it seems that microlaparoscopic pyloromyotomy is safe and feasible with the lowest rate of complications and the shortest operative time. The Bianchi approach is a good alternative to achieve a small scar without laparoscopy.

Keywords Microlaparoscopy · Pyloromyotomy · Circumbilical · Open pyloromyotomy

Introduction

The use of conventional laparoscopy for pyloromyotomy as compared with the open technique and the Bianchi approach in children with infantile hypertrophic pyloric stenosis (IHPS) is discussed controversially in the recent literature.[1–7] The results in several randomized comparative studies highlighted similar outcomes in terms of the operative time and the overall complication rate for the conventional laparoscopic and the open pyloromyotomy approaches, somewhere resulting in recommendations in favor of the open approach. However, the recent meta-analysis published by Sola and Neville[2] reported an overall benefit of the laparoscopic approach. Here, we attempt to further improve the efficacy of the laparoscopic approach with respect to shorter operative time, technical simplification, and reduced access traumatization following microlaparoscopic pyloromyotomy. The aim was to further minimize access trauma and to downsize the instruments involved, in particular, the scopes used for the laparoscopic pyloromyotomy in children. Microlaparoscopic pyloromyotomy involves the

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exclusive use of the 2-mm instrument sets and the small-diameter scopes, 1.7 to 2.4 mm in diameter. Over the last three and a half years, we implemented the new minimally invasive technique for pyloromyotomy—the microlaparoscopic approach—in a prospective study.[8]

To date, the microlaparoscopic pyloromyotomy has not been compared with the open approaches. This retrospective study compares the surgical results and the outcomes of the microlaparoscopic approach to the open techniques of the right upper quadrant access and of the circumbilical approach for pyloromyotomy.

Methods

We conducted a retrospective comparative analysis of the surgical charts of 110 infants undergoing pyloromyotomy either microlaparoscopically (MLP), through the circumbilical approach (UMB), or via right upper quadrant (RUQ) access for IHPS. We studied patients who underwent surgery at one of the two departments of pediatric surgery (Mainz and Trier) in Germany. We reviewed infant records spanning a period of 10 years; the patient's age, sex, weight, operating time, length of stay, number of postoperative emeses, conversion/complication rate, and surgical outcomes. The data from the microlaparoscopic pyloromyotomy group were collected during a continuous prospective, non-randomized study (the initial results of the first 21 cases are reported in[8]). The patients for the newly introduced technique of microlaparoscopy were randomly assigned according to the availability of the microlaparoscope and to the experience of the consultant surgeons in microlaparoscopy.

The diagnosis was made according to characteristic clinical appearance and confirmed by ultrasound. Dehydration and metabolic alkalosis were corrected before surgery. All procedures were performed under general anesthesia with endotracheal intubation.

Variables were compared between the three surgical approach groups. Statistical analysis was performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IBM Group). Statistical significance was assumed in the case of p values less than 0.05. The non-parametric testing was performed using the Mann–Whitney U test. The linear regression analysis was performed where appropriate. Power estimate for study design was 0.8 or above; no power calculation was performed in non-parametric testing.

Surgical Procedures

The open approach was performed with a standard Weber–Ramstedt technique, which involves a transverse skin incision and division of the right rectus abdominis muscle. The UMB was performed through a curvilinear incision in the right lateral umbilical crease followed by a vertical fascial incision through the linea alba. The pylorus was delivered through the incision, and the extracorporeal pyloromyotomy was performed; or alternately, the pylorus remained in the peritoneal cavity and intracorporeal pyloromyotomy was performed.

For the microlaparoscopic pyloromyotomy, a 2-mm instrument set and a 2.4-mm miniscope were used (except for the first ten cases, for which a 3-mm pylorus spreader was used). The surgical technique for microlaparoscopic pyloromyotomy has been previously described in detail.[8]

Results

This study included 110 children (85 boys and 25 girls, age range from 10 to 98 (average 28)days) from the two departments of pediatric surgery (Mainz and Trier), Germany, undergoing pyloromyotomy for IHPS. The microlaparoscopic approach was performed in 28 children (time period, 2006–2010; laparoscopic pyloromyotomies using a 5-mm scope for the visualization were excluded). Twenty-six children were operated upon using the open technique (Weber–Ramstedt) between 2000 and 2004. The circumbilical approach (Bianchi) was performed in 56 children (three in Mainz (2004–2005), 53 in Trier (2004–2009)). There was no significant difference in age, weight, or sex among the three groups. Detailed demographic data and preoperative ultrasound measurements of the pylorus for each group are expressed in Table 1.

There was a significant difference between Bianchi and microlaparoscopy in operation time (average 38.5 vs. 20.5 min, $p<0.0001$; Fig. 1) and time to full enteral feed (average 48 vs. 32 h, $p=0.001$). There was no significant difference in postoperative length of stay (75 vs. 82 h, $p=0.12$) when comparing the Bianchi approach and microlaparoscopy.

The microlaparoscopic approaches performed by residents generally represented their first attempts at laparoscopic pyloromyotomy. The operative time among surgeons experienced with microlaparoscopy was shorter (14 vs. 30 min for residents, $p<0.0001$).

The operative time ranged from 9 to 18 min (average of 14 min) for the consultant surgeons. When comparing the Weber–Ramstedt procedure and microlaparoscopy, microlaparoscopy resulted in significantly shorter operative time (50 vs. 20 min, $p<0.0001$), a shorter time to full enteral feed (70 vs. 32 h, $p<0.001$), and a shorter postoperative length of stay (90 vs. 82 h, $p=0.04$).

Complications

Prolonged vomiting after the first postoperative day occurred in 13 patients in the circumbilical approach group, four patients with microlaparoscopy, and five patients with

Table 1 Demographic data of the three compared cohorts (microlaparoscopically (MLP), through the circumbilical approach (UMB) and via right upper quadrant (RUQ))

Approach	Average			Min/max (SD)		
	MLP	UMB	RUQ	MLP	UMB	RUQ
Age (days)	37	38	46	17/80 (17.29)	16/76 (13.73)	10/98 (22.66)
OP time (min)	20.5	38.5	50	9/36 (7.5)	21/65 (10.3)	30/113 (23.3)
Overall LOS (h)	98	99	99	36/180 (64.22)	39/180 (64.22)	39/180 (64.22)
Postoperative LOS (h)	82	75	90	17/160 (51.3)	26/160 (51.3)	26/160 (51.30)
Pyloric muscle thickness (mm)	4.6	4.8	5.2	3/6 (0.89)	3/6 (0.85)	4/6.6 (1.05)
Pyloric length (mm)	18.2	19.5	20	12/24 (5.0)	14/26 (2.6)	13/25 (3.5)
Pyloric cross-sectional diameter (mm)	12.5	18.7	15	9/16 (2.39)	12/27 (2.39)	12/18 (1.9)
Weight (g)	3,761	3,931	4,088	2,400/5,370 (739)	2,240/5,730 (788)	2,730/6,360 (946)
Time to full enteral feeding (h)	32	48	70	17/72 (18.3)	17/72 (18.3)	58/120 (81)

the Weber–Ramstedt procedure. The reported cases of postoperative vomiting are not suspected to be drug-induced, as morphine was not administered as a postoperative analgesia.

There were no cases of mucosal perforation or incomplete pyloromyotomy, duodenal stenosis, or readmission within 4 weeks after surgery in any of the three groups. There were four cases of small-wound hematoma periumbilically and one case of wound infection in the group that underwent the circumbilical approach. There were two cases of systemic inflammatory response syndrome in Weber–Ramstedt patients. No such complications occurred in the microlaparoscopy group. In Table 2, the results of the study presented are expressed, and an overview to the recent literature (prospective randomized study, retrospective study, and meta-analysis) is given. A direct comparison of our data to the selected different level studies in the literature in this table is not mentioned since they are of very different methodology.

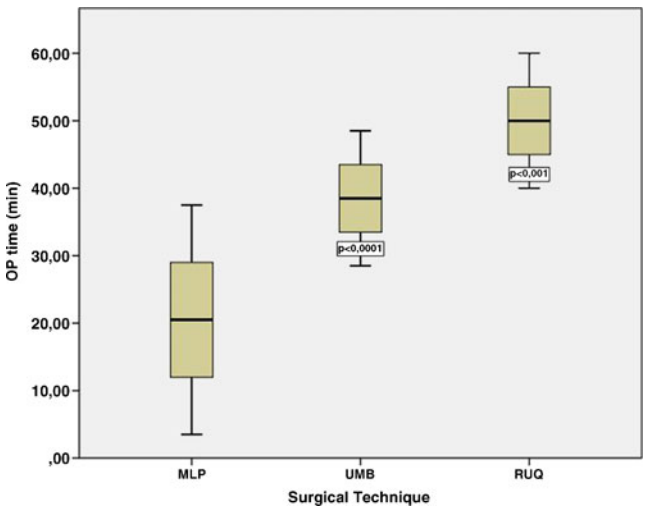

Fig. 1 Comparison of OP time in three indicated methods: microlaparoscopically (MLP), the circumbilical approach (UMB), and via right upper quadrant (RUQ)

For all children operated upon microlaparoscopically, we performed clinical re-examination as follow-up. The time to follow-up averaged 8 weeks; particular attention was paid to postoperative scar appearance. Among 27 children, the parents were unable to identify the 2-mm port insertion in the abdominal wall, except for the first ten cases, for which a 3-mm pylorus spreader was used.

Discussion

Extramucosal pyloromyotomy performed through a transverse skin access at RUQ has been practiced for nearly a century essentially unchanged, with a high level of efficacy and low rate of intra- and postoperative complications. The one matter remaining to be resolved with respect to this approach is the cosmetic appearance of the scar.

Efforts to achieve improved cosmesis with the extramucosal pyloromyotomy surgical approach include circumbilical access as described by Tan and Bianchi[9] in 1986 and laparoscopic access as first described by Alain et al.[10] in 1990. The circumbilical approach results in superior cosmesis as compared with the RUQ approach but involves technical difficulties in achieving umbilical access to reach the pyloric olive. Wound infection, hematoma or stitches granuloma, incisional hernia, and laceration of the gastric and duodenal serosas associated with UMB are reported infrequently in the literature. The attempts to refine UMB are described by Gauderer[11] as transumbilical intracavitary pyloromyotomy, by Yokomori et al.[12] as pyloromyotomy through a sliding umbilical window, by Lazar et al.[13] as transumbilical pyloromyotomy with umbilicoplasty, and by Alberti et al.[14] as a right semicircular umbilical skinfold incision.

Table 2 Results of the present study and an overview of the recent literature

	Present study, retrospective, two centers			Muensterer[25] (retrospective, single-surgeon, n=15)		Hall et al.[3] (double-blind, randomized, multicenter)		Perger et al.[4] (retrospective)			Meta-analysis by Sola[2a]
	Microlaparoscopy	Bianchi	Weber–Ramstedt	Single-incision (SIPES)	Conv. lap.	Laparoscopic	Open	Laparoscopic (LAP)	Umbilical (UMB)	Right upper quadrant (RUQ)	Laparoscopic (LP) vs open (OP)
	n=28	n=56	n=26	n=15	n=15	n=87	n=93	n=133	n=246	n=243	
OP time in average (min)	20.5±7.5 (for consultant surgeon, 14±5)	38.5± 10.3	50±23.3	30.3±15.8	21.7± 9.9.	30	32	42±16	52±16	44±12	No statistically significant difference in operating time (MD, 0.49 min[−0.94, 1.92]; p=0.50)
Incomplete pyloromyotomy	0	0	0	0	0	3	0				6 patients in LP (OR, 7.74 [0.94, 63.38]; p=0.06)
Mucosal perforation	0	0	0	2	0	2	1	1	2	0	4 patients (1.3%) in the LP group and 3 patients (0.9%) in the OP group (OR, 1.29 [0.34, 4.86]; p=0.70)
Conversion rate to open approach	0	–	–	0	0	0	–	1	–	–	5 (1.7%)
Wound infection/ hematoma	0	5	2	0	0	6	9	1	8	3	OP had an excess wound complication rate of 58% (OR, 0.42 for LP [0.20, 0.91], difference was statistically significant (p=0.03))
Time to full feeding (h)	32±18	48±18	70±31			18.5 median	23.9 median	Data not provided			LP had shorter time to full feeding (MD, −11.52 h [−12.77, −10.27]; p<0.00001)
Prolonged postoperative emesis (number of patients)	4	13	5			43	52	The LAP group was superior to both RUQ and UMB (p=0.002 and p=.002, respectively, postoperative emeses while in-patient)			No statistically significant difference in the rate of postoperative vomiting between the two groups
						Number of infants who have at least one significant vomit					
Length of postoperative stay (h)	82±51	75±51	90±51	1.1±0.3 days	1.1± 0.5	33.6	43.8	33±23	32±21	35±24	LP shorter postoperative LOS (MD, −5.71 h [−8.90, −2.52]; p=0.0005)

[a] Includes six prospective studies (five level I, one level II) with 625 (303 LP, 322 OP) patients

There have also been attempts to improve the laparoscopic approach with procedural refinements.[15–17] In agreement with a willingness-to-pay analysis performed by Haricharan et al. (2008),[18] the cosmetic benefit of laparoscopic pyloromyotomy was evaluated in 416 subjects. Among those surveyed, 85% was willing to pay additional fees for their children to have smaller scars. The use of only 2-mm instruments in the case of the microlaparoscopic approach leads to superior cosmesis. This report does not include a statistical analysis of value and cosmesis achieved, but current studies are underway.

The increasing numbers of retrospective or even prospective randomized comparative studies have compared these three pyloromyotomy access approaches. However, in terms of surgical complications and technical errors (e.g., feasibility, operative time, mucosal perforation, incomplete pyloromyotomy, wound infection, or incisional hernia), as well as in terms of outcome sources (e.g., time to full enteral feeding, postoperative vomiting episodes, postoperative length of stay) and cosmesis achieved postoperatively, the value of the laparoscopic approach as well as that of the open techniques is a source of controversy among pediatric surgeons. In 2004, a meta-analysis of reported studies by Hall et al.[19] was unable to show a clear benefit of laparoscopic approach in comparison to the open techniques. In a recent meta-analysis of the data from five level 1 studies and one level 2 study by Sola and Neville[2], the authors identify a positive trend toward the laparoscopic approach with a significantly reduced rate of total complications. While this meta-analysis does favor the laparoscopic approach on the basis of a reduced rate of total complications, the authors clearly comment that this result is predominantly due to a difference in the rate of wound infection between the groups.

Our retrospective comparison of the recently introduced microlaparoscopic pyloromyotomy approach as compared with the Bianchi and Weber–Ramstedt approaches does not have sufficient statistical power for any scientific conclusions. The present report comparing the results of microlaparoscopic pyloromyotomy to the open procedures performed at two pediatric surgery departments can be seen strictly as a preliminary analysis of institutional experiences. Since the present report is a retrospective analysis, the issue of the timeline regarding the different protocol for feeding regimes for the RUQ cohort makes a comparison difficult. Anesthesia and feeding regimes for the MLP and Bianchi cohorts were identical in both centers included in the study (Mainz and Trier). The procedures were performed within the same time period. However, despite the small sample size, we conclude that microlaparoscopic pyloromyotomy is superior to the open techniques with respect to operative time, total complication rate, and time to full feeding (Table 1). The benefits of microlaparoscopy in comparison to conventional laparoscopic pyloromyotomy include the improvement and refinement of procedural technique, including: (1) a one-line incision of the sero-muscular layer using a high-power monocautery knife, (2) use of a 2-mm Babcock grasper instead of a 3-mm pyloric spreader, and (3) reduced access traumatization. Both the laparoscopic and the circumbilical techniques for pyloromyotomy have good results in experienced hands.

Over the last year, the microlaparoscopic pyloromyotomy approach has become a routine procedure at the Department of Pediatric Surgery in Mainz. Innovative techniques in the minimal invasive surgery, e.g., natural orifice transluminal endoscopic surgery and single-port laparoscopy (SPL) are becoming increasingly popular for the adult patients. Also, in the field of minimally invasive pediatric surgery, the use of the single-site surgery (including the synonyms: SPL, single-incision laparoscopic surgery, laparo-endoscopic single-site surgery, or even single-incision pediatric endosurgery (SIPES), a term adopted in pediatric surgery) has been reported in recent literature.[20–24] Muensterer[25] recently reported a retrospective comparison of pyloromyotomy performed by SIPES technique and by conventional laparoscopy. The two reported mucosal perforations in the SIPES cohort (15 infants) in this report may be attributed to the initial learning curve of a new technique. However, there are substantial disadvantages of the SIPES technique compared with the microlaparoscopy, particularly in the case of pyloromyotomy. (1) The microlaparoscopic approach preserves the proven beneficial principle of triangulation, in contrast to the SIPES technique with its technical challenges and difficulties, e.g., clashing instruments, trocar crowding, and in-line endoscope viewing. (2) In the case of SIPES, the need for a 1.5- to 2.5-cm large umbilical incision and, subsequently, the traumatization of the fascia do not comply with a minimally invasive procedure, particularly among infants. For instance, the same size incision is used in the open technique of circumbilical pyloromyotomy. The question arises as to whether this size of access is still minimally invasive (especially in the case of infants), or if the “minimal invasive” is only attributed to the use of laparoscopic instruments. In the case of microlaparoscopy, the use of the 2-mm instrument sets and miniscopes results not only in a nearly scarless cosmesis but also reduces the access traumatization mainly to a minimum. (3) The limited number of working ports in SIPES is not a concern in the microlaparoscopy, nor is the choice of port positions restricted. (4) Operative time needed for creating access and for the closure of the access at the end of the procedure is very short in microlaparoscopy, since the ports are punctured into the

abdominal wall and simply removed at the end of the procedure. There is no need for incision or for suturing of the fascia and skin, as is the case in SIPES. Other disadvantages in SIPES, such as the large size of current proprietary multitrocar devices and instruments and longer procedural operative time at present, can be positively improved with further development of the technique in the future. The detailed results of the SIPES pyloromyotomy from the above-mentioned report are confronted in the results of the present report in Table 2. A direct comparison of both methods is not addressed in this paper, nor does it seem to be appropriate at this time, as the published data of microlaparoscopic and SIPES pyloromyotomy are from pilot–feasibility studies.

Conclusion

Despite the small sample size in the present study, it seems that the microlaparoscopic pyloromyotomy is safe and feasible. This technique results in the lowest rate of complications and the shortest operative time. The Bianchi and Weber–Ramstedt approaches were associated with longer operative time and length of postoperative stay.

Microlaparoscopic pyloromyotomy is the standard routine approach in Mainz, while the Bianchi approach is preferred in Trier. This discrepancy is merely the result of institutional preferences. In summary, the fact is that if you can do the microlaparoscopic operation safely, these children will mature with no evidence that an operation occurred, which is associated with a minimum of access trauma at present.

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ORIGINAL ARTICLE

Quality of Life in Patients After Pancreaticoduodenectomy for Chronic Pancreatitis

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Abstract
Purpose Pancreaticoduodenectomy (PD) is the most frequently performed resectional procedure in chronic pancreatitis. Only a few studies have evaluated quality of life (QOL) after PD for chronic pancreatitis. This retrospective study examined long-term quality of life and relief of symptoms in a homogenous consecutive cohort of 67 patients undergoing PD for chronic pancreatitis.
Methods A standard QOL questionnaire was sent to 168 patients after PD who had undergone PD for chronic pancreatitis at the University Hospital Dresden between 1994 and 2008. QOL and long-term sequelae were evaluated by the EORTC quality of life questionnaire supplemented with complementary questions. Results were compared to general population data based on large random samples.
Results Median follow-up was 69.1 months. Complete response was obtained from 67 (48.5%) patients. Long-term survival of our patients was lower than expected rates based on the Federal Republic of Germany life table analysis ($p<0.001$). There was an improved pain control and an increase in weight gain. Overall, QOL scores were slightly inferior to those of the control group. A common problem after PD was onset of diabetes mellitus; however, exocrine function of the pancreas was stable.
Conclusions This is the largest single-institution experience assessing QOL after PD for chronic pancreatitis. Most patients have QOL scores comparable to those of the control patients and can function independently in daily activities.

Keywords Surgery · Chronic pancreatitis · Long-term follow-up · Pancreaticoduodenectomy

Introduction

Chronic pancreatitis is a disease characterized by persistent severe abdominal pain, progressive pancreatic endocrine and exocrine insufficiency and possibly mechanical complications. The disease is frequently the result of chronic alcohol abuse, and patients are often addicted to narcotics at the time of the presentation to a surgeon. The treatment of chronic pancreatitis remains a challenging problem. The success of long-time conservative therapy is uncommon.[1,2] Although initial patient management should be supportive and conservative, operative intervention will be required for selected subgroups of patients. A broad spectrum of surgical procedures has been applied, aiming primarily at the relief of pain and the management of complications associated with chronic pancreatitis.

Pancreaticoduodenectomy (PD) is gaining acceptance as an appropriate procedure for these purposes.[3,4] Today, PD is performed with complication rates less than 40% and with mortality below 5%.[5,6] Because PD is frequently performed in chronic pancreatitis, there are increasing numbers of PD long-term survivors who have recovered from the procedure.

Many studies focusing on the effects of PD on the physiology of the digestive tract and its impact on the QOL of the patients consider malignant as well as benign diseases.

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These studies can naturally not focus on the special background of patients with chronic pancreatitis. Only few studies have considered long-term results of PD in a homogenous cohort of patients with chronic pancreatitis so far.[1,7,8] In the present study, we present results of 168 patients undergoing PD for chronic pancreatitis in the Visceral, Thoracic and Vascular Surgery of the University Hospital Dresden.

Because of the high numbers of PD in chronic pancreatitis, information about the long-term results of this operation is desirable. The current study was designed to assess the mortality rates, QOL, relief of symptoms, employment and long-term sequelae of a homogenous cohort of patients after PD and to provide a comparison with healthy controls.

Patients and Methods

Patients

Patients undergoing PD have been prospectively entered into a computerized database since 1994 in the Clinic for General, Thoracic and Vascular Surgery at the Carl Gustav Carus University Hospital, Dresden. Eight fellowship-trained pancreato-biliary surgeons performed 672 consecutive PDs between October 1993 and November 2008. The final pathological diagnosis confirmed chronic pancreatitis in 168 (25%) of these patients. We used the database to identify those patients. Patients were contacted by mail or telephone and asked to participate in our survey. Data were complemented by physicians' and surgeons' office notes. The information for patients who died was obtained from family members or the general practitioner. Thirty patients had died at the time point of our study. Complete response was obtained from 67 (48.5%) patients. Apart from survival, for which we included all patients, these 67 patients are considered as our study cohort.

Surgery

Head resection included 96 pylorus-preserving pancreatoduodenectomies (PPPD) and 72 standard Whipple–Kausch pancreatoduodenectomies (Whipple). Indications for head resection were pain, mechanical complications of chronic pancreatitis and suspicion of malignancy. Reconstruction in PPPDs was performed with a single jejunal loop. Pancreatojejunostomy was achieved in end-to-side "dunking" technique using two rows of suturing with absorbable material. Hepaticojejunostomy was performed using one-row and all-layer interrupted suture with absorbable monofilamental material (5–0 to 6–0). Duodenum-preserving head resections were not considered in the actual study to achieve a homogenous patient cohort.

Instrument

The EORTC QLQ-C30 is a self-administered core questionnaire. It is intended to measure general aspects of QOL specific to cancer patients and consists of 30 items.[7] Each item is scored in four categories from (1) 'Not at all', (2) 'A Little', (3) 'Quite a bit' and (4) 'Very much' with the exception of items in 'Global QOL' scale, which range from (1) 'Very poor' to (7) 'Excellent'. The items are combined to five functional scales 'Physical functioning', 'Role functioning', 'Cognitive functioning', 'Emotional functioning', 'Social functioning' and 'Global QOL'. The questionnaire also includes three symptom scales 'Fatigue', 'Pain' and 'Nausea and vomiting' and six single-item scales 'Dyspnoea', 'Insomnia', 'Appetite loss', 'Constipation', 'Diarrhoea' and 'Financial difficulties' due to disease or treatment.[9] The questionnaire was supplemented by 20 self-designed questions concerning actual clinical symptoms, drug consumption and social aspects like marital status, employment, new onset of diabetes and clinical signs of exocrine insufficiency.

Data Collection

The medical records from a prospective database of patients who underwent PD for chronic pancreatitis were analysed retrospectively for each case. In accordance with the guidelines for human subject research, approval was obtained from the Ethics Committee at the Carl Gustav Carus University Hospital. Preoperative parameters included patient demographics, general condition, nicotine and alcohol abuse, co-morbidities (hypertension, diabetes, others), symptoms and course of chronic pancreatitis (exocrine insufficiency, pain, obstructing complications of pancreatitis, weight loss), comprehensive laboratory tests (e.g. CRP, bilirubin, creatinine, amylase, lipase and others), prior imaging studies and indication for operation. Preoperative medical imaging included ultrasound, CT and MRCP imaging to define underlying ductal disorders in patients undergoing operation for chronic pancreatitis. ERCP and sphincter of Oddi manometry were not routinely utilized in the preoperative evaluation of this patient group.

Postoperative events like complications were also recorded prospectively and analysed retrospectively. BMI for normal population was retrieved from the homepage of the Federal Statistical Office of the Federal Republic of Germany. Alcohol-induced chronic pancreatitis was assumed in individuals with chronic pancreatitis when alcohol was consumed in a daily basis.

Statistical Analysis

The values given on the items within each scale were summated. According to EORTC Scoring Manual, raw

scores were linearly transformed in order to produce standardised scores ranging from 0 to 100. High scores for functional scales indicate high level of functioning whereas high scores for symptom scales/items represent high level of symptoms/problems. These scores can be compared to normal standards of control subjects.[10,11] Values are expressed as mean±standard deviation. The estimates of patient survival were made using the method of Kaplan and Meier. The expected survival rates were calculated based on life tables for the population of the Federal Republic of Germany. Comparisons of survival were made using the log rank. Student *t* tests and Fisher's exact tests were used for comparisons between groups, and a *p* value <.05 was considered significant. Statistical computations were performed using Excel (Microsoft) and PASW Statistics 18.0 for Windows (Chicago, IL, USA).

Results

Patient Demographics and Mortality

A total of 168 eligible patients were entered in the database during the study period. The follow-up of the patients showed that 30 patients had died at the time of follow-up. Complete quality-of-life data were obtained from 67 of the 138 residual patients (48.5%). Mean follow-up was 69.1 months (±3.96 months). Of the 67 patients, there were 12 females and 55 males; 41 patients underwent PPPD and 26 patients underwent Whipple. The average overall age was 49.54 years (range 32–75).

The etiology of chronic pancreatitis was alcohol abuse in 47 patients (70.1%), idiopathic disease in 15 (22.4%), biliary in two (3.0%), pancreas divisum in one (1.5%) and hereditary in two (3.0%). The diameter of the pancreatic duct as measured by MRI in our cohort (n=67) was 5.41 mm (4.71–6.11 95%CI). Of the ducts, 34.3% (n=23) were 7 mm or less of diameter. Eleven of the patients had stones in the duct.

Demographic data are presented in Table 1. The chief complaints and indications for surgery were pain of varying intensity (92.5%), obstructive jaundice (28.4%), gastric outlet obstruction (16.4%), and suspicion of malignancy (6.0%; multiple answers are possible). Fifty-five patients (82.1%) had more than two admissions to hospital for treatment of pancreatitis before surgery.

As mentioned above, 30 patients died during follow-up. One patient (0.6%) died postoperatively because of septic multi-organ failure following septicemia with an unidentified focus. There were 29 late deaths: eight deaths were related to alcohol abuse, eight to neoplasm, four were unrelated to the operation or chronic pancreatitis, and nine died from unknown causes (Table 2). Observed survival was lower than the expected based on the Federal Republic of Germany life tables (p<0.0001; Fig. 1).

Table 1 Demographic and clinical data of the patient cohort

Demographic data (Pancreaticoduodenectomy (n=67))	n (%)
Age, years (range)	49.54 (32–75)
Gender	
Male	55 (82.1)
Female	12 (17.9)
Etiology	
alcohol-induced	47 (70.1)
idiopathic	15 (22.4)
biliary	2 (3.0)
Pancreas divisum	1 (1.5)
hereditary	2 (3.0)
Type of resection	
Whipple	41 (61.2)
PPPD	26 (38.8)
BMI	22.2 (±3.46)
General condition	
Good	39 (58.2)
Mediocre	26 (38.8)
Poor	2 (3.0)
Nicotine	57 (85.1)
Alcoholism	53 (79.1)
Diabetes mellitus II	22 (32.8)
Insulin dependent	12 (17.9)
Non-insulin dependent	10 (14.9)
Exocrine insufficiency	40 (59.7)

Relief of Pain

Median duration of pain before surgery was 43.8 months (±4.79 months), with pain located in the upper abdomen (46.3%) or the back (26.9%); belt-like pain occurred in 16.4% of the patients. Only five patients (7.5%) were pain free before operation and had resection for other purposes. Sixty-two (74.6%) of our patients were dependent on narcotic analgesics before operation.

At the time of follow-up, 23 patients (35.4%) had no pain at all, 33 had less pain than before operation (50.8%), five had no change in pain (7.7%) and in four patients (6.1%), the pain worsened. Two patients did not comment on this question. Twenty-three patients of our study cohort had regular narcotic intake. Of these, one was in the group without pain (4.3% of this group), 15 were in the group with less pain than before operation (45.5% of this group) and four in the group without change in pain (80.0% of this group). Three patients in the group with more pain than before operation regularly took pain killers (75.0% of this

Table 2 Chronic pancreatitis: causes of death in long-term follow-up after pancreatic head resection

Alcohol-associated	
Cirrhosis and cardiac insufficiency	1
Cirrhosis	2
Hemorrhage	1
Hypoglycemia during alcohol intoxicaton	1
C2-Intoxication	2
Suicide	1
Perioperatively	
Septicemia after operation	1
Neoplasia	
Pharyngeal cancer	2
Esophageal cancer	1
Lung cancer	1
Oral cancer	1
Colorectal cancer	1
Hypopharyngeal cancer	1
Laryngeal cancer	1
Unknown cause (Relatives/GP)	9
Others	
Empyhsema	1
Pulmonary embolism	1
Peritonitis caused by a percutaneous transhepatic drainage	1
Heart attack	1
	30

group). Interestingly, subgroup analysis showed that of five patients without any pain before operation, two (40%) had subjectively more pain at the time of follow-up (Fig. 2a, b).

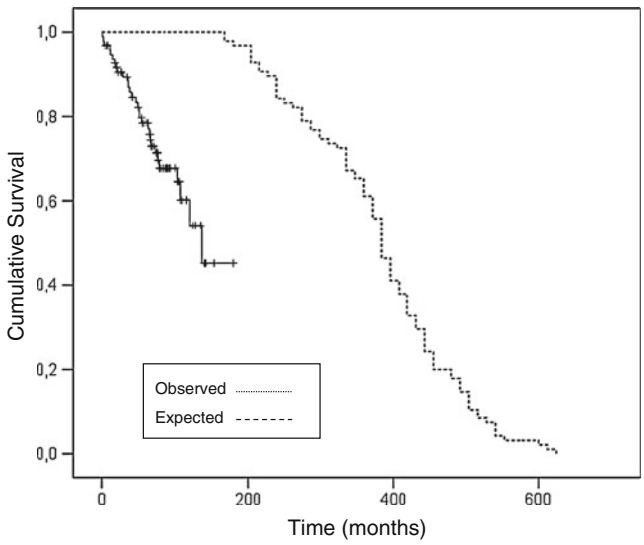

Fig. 1 Actuarial survival of patients with chronic pancreatitis treated by a pancreatic head resection compared to expected survival based on the Federal Republic of Germany life tables

Pancreatic Exocrine Insufficiency and Gastrointestinal Symptoms

Exocrine insufficiency was observed in 40 (59.7%) of the patients preoperatively. After operation, only 35 (52.2%) patients showed exocrine insufficiency with dependency on enzyme substitution. Postoperative problems with digestion were minimal according to the answers in the EORTC questionnaire. Respondents scored only 22.7 for the item "appetite loss" (5.7 in healthy controls), 7.5 for "Constipation" (7.1 in healthy controls), 15.6 for "Nausea" (2.9 in healthy controls) and 23.2 for "Diarrhea" (9.3 in healthy controls), which indicates a good intestinal functioning.

Additionally, answers to our complementary clinical questions did not show an adverse effect on digestion: 20 patients (29.9 %) had one to three meals per day, 42 (62.7%) had four to five meals per day. Only three patients had more meals per day than this.

Stool frequency was one to two times per day in 45 of the patients (61.2%), only 16 patients (23.9%) reported a stool frequency averaging more than two stools per day. Mostly, stool consistency was normal (67.2%). Forty-four (65.7%) patients reported good appetite (16 patients with mediocre appetite, five with bad appetite).

Weight Maintenance or Gain

Mean BMI of our study group was 22.2 (±0.42). Fifty of our patients (74.6%) experienced weight loss before operations, with an onset of 7.7 months before operation (±1.16 months). Mean weight loss was 8.85 kg (±0.87 kg). In ten of the patients (14.9%), this weight loss due to pain or intra-abdominal complications of chronic pancreatitis had direct influence on the decision to operate. In this subgroup, BMI was 20.2 (±0.85) and weight-loss was 11.5 kg (±1.51).

Twenty-eight of our patients gained weight after operation (41.8%), 17 had unchanged weight (25.4%) and in 19 patients, weight worsened after operation (28.4%). Three patients did not comment on their weight.

Subgroup analysis showed that weight change did not correlate with preoperative weight. Similarly, weight change did not correlate with etiology of chronic pancreatitis or postoperative pain relief or exocrine or endocrine functioning.

Endocrine Functioning

Before surgery, 23 (34.3%) patients had diabetes. Twelve patients (16.4%) were insulin-dependent, four (5.9%) were on oral anti-diabetics and seven (10.4%) were treated dietary. The mean duration of diabetes before operation was of 29.9 months (±7.1 months).

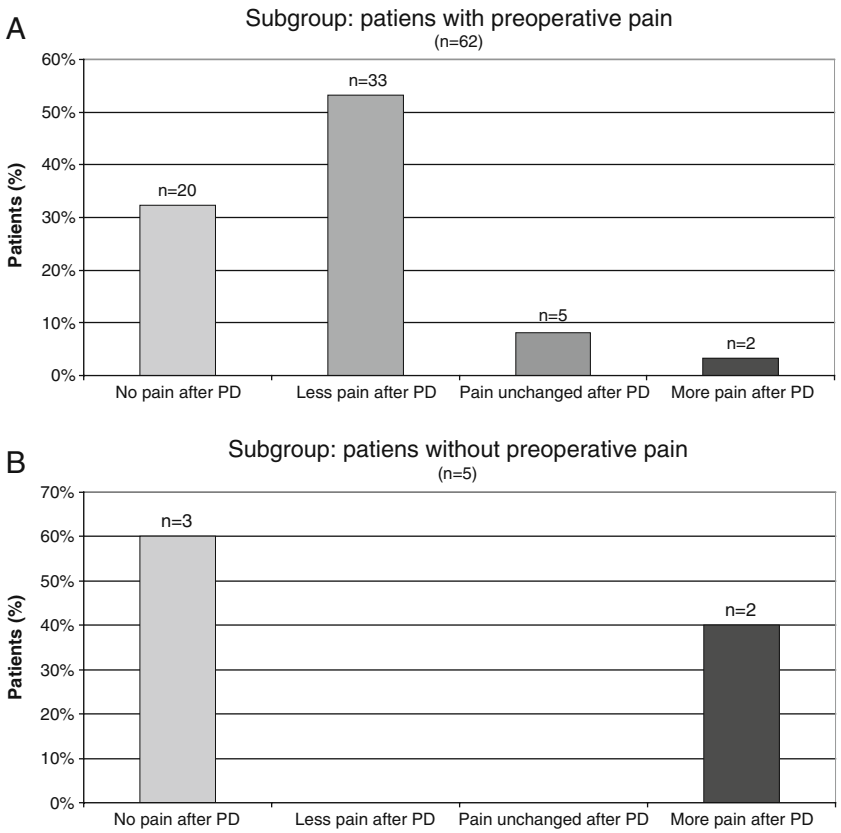

Fig. 2 Subgroup analysis comparing the development of postoperative pain in patients with (**a**) and without (**b**) preoperative episodes of pain

Postoperatively, a new onset of diabetes was seen in 16 (23.8%) of the patients; however, three patients improved their dietary-treated diabetes after surgery and were normoglycemic again.

This resulted in a postoperatively number of 36 (53.7%) diabetic patients. Twenty-eight (41.7%) were insulin-dependent and six patients (8.9%) were treated orally. Two patients did not comment on the status of their diabetes in the follow-up (Fig. 3).

Alcohol and Nicotine

Fifty-three (79.1%) were addicted to alcohol before operation. At the time of follow-up, the number decreased to 25 patients (37.3%). Smoking was seen in 57 of the patients (85.1%) preoperatively and 47 of the patients (70.1%) after PD.

Social Status

At the time of follow-up, 15 patients were unemployed (22.4%), 17 were working (25.4%) and 32 (47.8%) were retired. Three patients did not comment on their present occupation. Twenty-one (31.3) of these patients did not work due to the impairment of health by chronic pancreatitis. Seven were unmarried (10.4%), 40 were married (59.7%), ten were divorced (14.9%) and seven were widowed (10.4%) at the time of follow-up.

Quality of Life

Complete quality-of-life data were obtained in 66 patients. The items of the three domains of the EORTC QLQ-C30 (functional scales, symptom scales, six single-item scales) were compared to normal individuals to evaluate differences between healthy subjects and our patients. Functional scales were generally lower than in a normal population. For mean scores of items, see Table 3.

To assess which social factors or health problems had the highest impact on quality of life, we correlated answers of our self-designed questions with 'Global Quality of Life' of the EORTC QLQ-C30. Those factors were employment status, marital status, weight gain, drug consumption (nicotine, alcohol), dependency on pain medication, medications for endocrine and exocrine insufficiency, symptoms of exocrine insufficiency, pain and ability to work.

We did not find a correlation of QOL with endocrine or exocrine insufficiency; however, we did see a statistical significant correlation of a high quality of life with patients who were pain free or had less pain after operation ($p=0.017$). Furthermore, patients without need for pain medication had a higher QOL ($p=0.02$). Interestingly, we also had a very good correlation between a high QOL and the ability to work ($p=0.02$). We further saw a trend

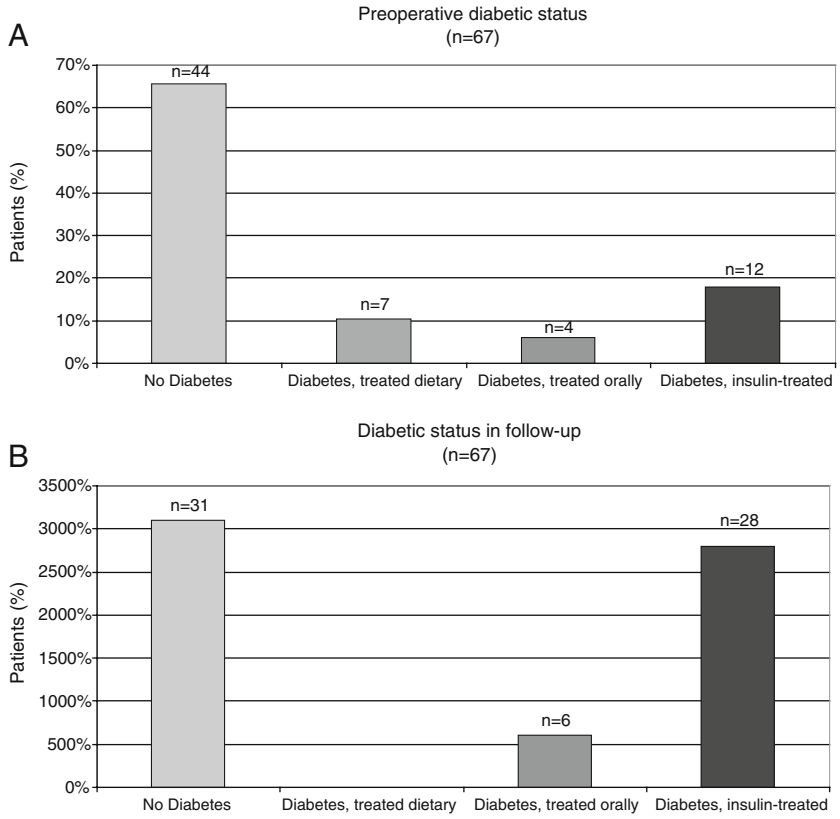

Fig. 3 Assessment of endocrine function of the pancreas preoperatively (**a**) and in follow-up (**b**)

towards a high QOL in married patients as well as patients reporting a good weight gain after operation. We did not see a correlation between abuse and QOL of life, although this could be ascribed to the high percentage of patients addicted to nicotine or alcohol in our cohort.

Discussion

PD is a common surgical procedure in the treatment of chronic pancreatitis. Because of this, there are increasing numbers of PD long-term survivors who have recovered from the procedure.

To make statements about the balance between the benefit of this surgical approach for pain control and weight gain and risks inherent to this procedure, we assessed mortality rates, QOL, relief of symptoms, employment and long-term sequelae.

We therefore analysed the so far largest homogenous cohort of patients with PD for chronic pancreatitis and compared results to healthy controls. Although we perform duodenum-preserving head resection in our Department, we

Table 3 The means (SD) of EORTC QLQ-C30 scales and items from our study compared to previous analysis of the long-term results in patients with chronic pancreatitis after pancreatic surgery and to normal population

Higher scores on functioning scales and Global Quality of Life represent better functioning. Higher scores on symptom scales and items represent more problems ("–" parameter not included in study)

		Dresden (2010, ±SD) $n=67$	Izbicki[13] $n=30$	Normal population[11]
Functioning scales	Physical functioning	78.2 (±2.9)	70	97
	Role functioning	76.5 (±3.9)	–	95
	Cognitive functioning	78.5 (±3.5)	66.7	94
	Emotional functioning	63.3 (±4.0)	66.7	87
	Social functioning	68.9 (±4.3)	66.7	97
	Global QOL	56.8 (±2.8)	57.1	87
Symptom scales	Fatigue	41.2 (±4.2)	33.3	18
	Pain	35.6 (±4.3)	0	11.9
	Nausea and vomiting	15.6 (±3.3)	0	2.5
Single items	Financial difficulties	43.4 (±4.5)	0	4.6

did not include those patients in this study to achieve a homogenous patient cohort.

Thirty patients died during follow-up. The observed survival was lower than expected based on the Federal Republic of Germany life tables. Interestingly, most of the deaths were directly or indirectly associated with alcohol consumption. We did further see a high percentage of patients with neoplasms of the upper gastrointestinal tract which are also correlated with nicotine and alcohol abuse. Mortality after surgery for chronic pancreatitis therefore appears to be owing in large part to the effects of alcohol abuse according to the previous studies.[7,12]

Of the 138 patients alive at the time of follow-up, 67 filled out the quality-of-life questionnaire and health habit survey. The low response rate of 48.5% may be due to the difficult social condition of most of the patients. The low response rate in patients with chronic pancreatitis is known and was already reported in previous studies.[1] Comparing the data of our study group with previous studies, we see more male patients and higher percentage of alcoholism.[1,7] This might be due to regional differences in alcohols consumption, but also different health systems.

The analysis of the patients' responses to our questionnaire rendered important information on the long-term quality of life and relief of symptoms.

As in other groups, we did see an improvement in pain control in 86.2% of the patients.[7,13] Although in nine of the patients no relief in pain was gained, one needs to consider the achieved success in the context of the patient's preoperative status of chronic pain in the majority of these patients. The conservative treatment of chronic pancreatitis achieves pain alleviation in less than 50% of the patients.[14] Our data therefore support the concept that the "pacemaker" of pain in chronic pancreatitis is located in the head of the pancreas and proximal pancreatectomy can achieve good pain relief.[15]

Exocrine function did not deteriorate significantly after operation; the number of patients with enzyme substitution was comparable before and after surgery. Enzyme substitution seems to be an acceptable treatment for exocrine insufficiency as only few patients complained about meteorism and/or high stool frequency. Furthermore, the incidence of meteorism was not correlated with restricted quality of life.

Weight loss is an important symptom of chronic pancreatitis. The weight loss is not only due to exocrine insufficiency, but also to severe chronic pain.[16] Indeed, a high number of our patients (74.6%) complained weight loss before surgery with a mean weight loss of 8.85 kg before surgery. The mean BMI was 22.2; this is much less than the average BMI in Germany of 26.3. However, during follow-up, 28 of our patients (41.8%) gained weight and this is in accordance to previous reports.[13]

Because endocrine function of the pancreas may deteriorate after resectional procedures, we also evaluated the impact of the operations on the diabetic status of our patients. Before surgery, 12 patients had insulin-dependent diabetes, four were on oral anti-diabetics, and seven were treated dietary.

Postoperatively, we saw improvement in the diabetic status of three dietary-treated patients. However, a new onset diabetes was seen in 16 (23.8%) of the patients. Twelve previous healthy patients developed insulin-dependent diabetes, and four developed diabetes with need for oral anti-diabetics. Additionally, several of the patients with preoperatively orally treated diabetes developed dependency on insulin. These data are not surprising, as it was already reported that patients with surgery for chronic pancreatitis display a worsened endocrine function in long-term follow-up.[1,7,8,12,13,17–20] However, it is still unclear if this deterioration is due to surgical intervention or if it is secondary to evolution of chronic pancreatitis.[21]

A very important point of the present study was to evaluate the global quality of life and to make statements about the balance of risks and benefits of the procedure for our patients. Global quality of life as determined by the EORTC QLQ-C30 was 56.8. Age-matched comparison with the data from Michelson et al.[11] showed that these scores were comparable with people suffering "some chronicle health problems". Previous report on head resection in chronic pancreatitis by Izbicki et al. shows a nearly identical score in long-term follow-up.[13]

To identify factors that might cause this impairment in QOL of our patients, we correlated QOL with different postoperative characteristics. A significant association with a high QOL was found in pain-free patients. There is furthermore a statistical significant correlation of patients without need of pain medication with a high QOL. Very interestingly, we also had a statistical significant correlation between a high QOL and the ability to work. There was no correlation of symptoms of exocrine insufficiency or diabetes mellitus with QOL.

These data suggest that pain relief and independency of analgesic drugs have a high impact on quality of life, while endocrine and exocrine insufficiency in follow-up do not significantly constrain QOL. The present study therefore supports surgery as adequate therapy in the treatment of chronic pancreatitis.

Conclusions

In conclusion, PD seems to be a good method for the treatment of selected patients with chronic pancreatitis to relief pain. QOL in operated patient is good and the complications of operation are tolerated well by the patients.

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ORIGINAL ARTICLE

Can Laparoscopic Pancreaticoduodenectomy Be Safely Implemented?

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Abstract
Introduction The implementation of laparoscopic pancreaticoduodenectomy (LPD) has been appropriately met with apprehension, and concerns exist regarding outcomes early in a program's experience. We reviewed our early experience and outcomes of LPD.
Methods A retrospective review of patients undergoing LPD was compared to a matched cohort of open pancreaticoduodenectomy (OPD) patients. The endpoints are as follows: age, gender, ASA score, BMI, operative time, estimated blood loss, perioperative transfusion requirement, intensive care unit stay, margin status, lymph node count, 90 day morbidity and mortality, length of stay, and adjuvant therapy treatment.
Results Fourteen patients underwent an attempted LPD. The median operative time was 456 min (interquartile range (IQR), 109.5), median estimated blood loss was 300 ml (IQR, 225), and 29% of the patients required a perioperative blood transfusion. A conversion was necessary in two patients (14%). A malignancy was present in 12 patients. The mean tumor size was 2.2 cm (standard deviation (SD), 1.1), the mean lymph node count was 18.5 (SD 6.2), and an R0 resection was achieved in all 12 cases. Clavien grade I/II complications occurred in 42% of the patients, and Clavien grade III/IV complications occurred in three (20%). There was one late postoperative death. The median length of stay was 8 days. Compared to OPD, LPD took longer to perform, but no differences were noted with respect to blood loss, morbidity, mortality, R0 resection rate, and LN harvest.
Conclusions LPD can be implemented in a high-volume pancreatic surgery center with acceptable oncologic and patient outcomes.

Keywords Pancreas · Pancreatic cancer · Pancreatitis · Whipple

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Introduction

Laparoscopic radical pancreaticoduodenectomy (LPD) had been met by an appropriate degree of skepticism following an initial report in 1994 by Gagner.[1] However, concerns regarding the feasibility and oncologic integrity of LPD have now been tempered by three recent reports of success[2–4], and others have generated enthusiasm through the utilization of robotic assistance to perform the procedure. Furthermore, a laparoscopic distal pancreatectomy has been successfully introduced into multiple high-volume pancreatic surgery centers with superior results.[5,6] In this setting, numerous centers are now considering the introduction of LPD with or without robotics to their pancreatic surgery programs.

Shorter hospital stays, reduced analgesia requirements, rapid return to baseline performance status, and reduced

morbidity have been observed in the laparoscopic treatment of various gastrointestinal malignancies.[6–9] Radical pancreaticoduodenectomy has been historically plagued by high rates of morbidity. This compromises the quality of life and precludes the administration of adjuvant chemotherapy to an unacceptably high number of cancer patients. Thus, the potential benefit of LPD compared to traditional, open techniques warrants exploration.

Due to the inherent learning curve required to master novel procedures, there are significant concerns that patient safety and operative outcomes will be compromised as surgeons with varying pancreatic and/or laparoscopic surgical experience begin to perform LPD, and the existing literature does not address this issue. To this end, we reviewed our initial experience with LPD as performed by a single, high-volume pancreatic surgeon with extensive laparoscopic surgical experience in a tertiary care setting. We present the preparation taken prior to the performance of LPD, the criteria utilized for patient selection and report on postoperative oncological surrogate markers and clinical outcomes. We conclude that laparoscopic pancreaticoduodenectomy can be safely implemented in a high-volume pancreatic surgery center without subjecting patients to an unacceptably higher risk of complications or a compromise of oncologic surgical principles.

Methods

A retrospective review of a prospectively maintained database was performed to identify all LPD performed at the University of Pittsburgh Medical Center (UPMC) between September 2008 and March 2010. An open pancreaticoduodenectomy (OPD) cohort matched for age, gender, comorbidities, body mass index (BMI), pathological diagnosis, and tumor stage was subsequently obtained from cases performed between January 2006 and August 2008. An approval by the University of Pittsburgh Institutional Review Board was obtained to perform this study, but was not required prior to the initiation of LPD given prior publication of the procedure. Rather a full disclosure regarding the surgical team's status with respect to LPD was provided to all of the patients. All cases were performed by a single surgeon (SJH) in conjunction with a surgical oncology fellow serving as first assistant. The primary surgeon is a high-volume pancreatic surgeon with extensive experience in minimally invasive surgical oncology having performed, exclusive of laparoscopic cholecystectomy, over 500 cases of minimally invasive procedures on the gastrointestinal tract, including gastric, hepatic, pancreatic, and colorectal resections.

Patient Selection

Patient selection was determined, in part, using the UPMC image-based mathematical model predictive of margin negative resection (R0).[10] This predictive model utilizes computed tomography (CT) and endoscopic ultrasound (EUS) imaging features to establish the probability of an R0 resection. All patients with lesions predicted by the model to have an increased risk of a positive margin and patients undergoing neoadjuvant therapy as part of a clinical trial were excluded.

Staged Development of Operative Technique and Experience

In order to achieve technical experience with LPD, the surgical team performed four LPD procedures on fresh frozen cadavers. These efforts focused upon trochar placement and methods of exposure and reconstruction. After comfort was reached in these regards, LPD resection with intentional conversion to standard open technique was performed on two patients. This step was taken to ensure an acceptable operative time for the resection (lap OR time <300 min), and to assess the adequacy of the resection by open technique. These patients were excluded from the current analysis.

Operative Technique

Port placement and utilization is depicted in Fig. 1. The sequence of the dissection is altered in that the inferior border of the pancreas and superior mesenteric vein dissection is performed prior to the Kocher maneuver. All arterial branches are controlled with clips or ligatures in addition to bipolar electrocautery or stapling. The uncinate process is dissected along the adventitia of the superior mesenteric artery. An antrectomy, rather than pylorus preservation, is routinely performed. The specimen is placed in a bag for retrieval. Additional prophylactic antibiotics are administered based upon the operative time prior to the formation of a muscle-sparing, right lower quadrant utility incision. A wound protector is also utilized.

For reconstruction, an end-to-side duct to the mucosa pancreaticojejunostomy is fashioned in two running layers of absorbable monofilament suture (polydiaxone) modified from the technique described by Ohwada.[11] An end-to-side hepaticojejunostomy using a running 4–0 polydiaxone suture is subsequently fashioned. The gastrojejunostomy is performed antecolic using a stapled technique. Two drains are routinely left in the vicinity of the pancreaticojejunostomy and the hepaticojejunostomy.

Endpoints

Data were obtained from both the electronic medical record and outpatient clinic charts and included operative time (minutes), blood loss (milliliters), intraoperative blood

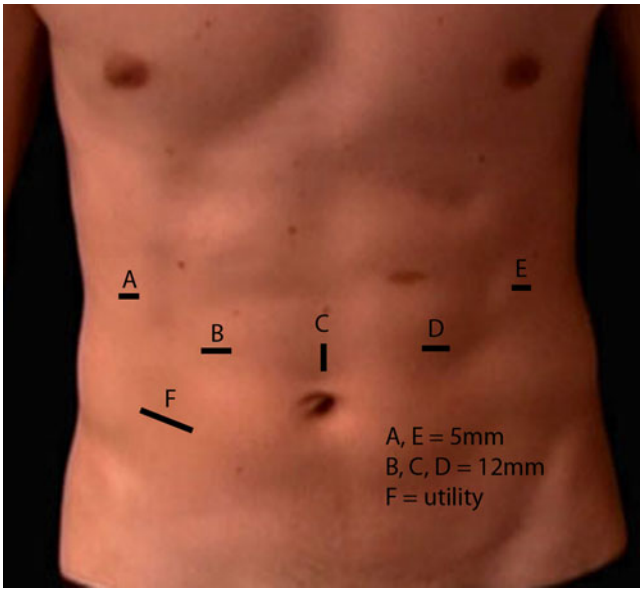

Fig. 1 The abdomen is entered using the Veres needle technique at port *E*. The remaining ports are placed under direct vision, and the camera is moved to port *C*. (1) Entry into the lesser sac, establishment of the plane between the middle colic and gastroepiploic vessels, mobilization of hepatic flexure/right colon, infrapancreatic portal vein dissection, and cholecystectomy: ports *D* and *E* with surgeon on the left. (2) Kocher maneuver, portal dissection, bile duct division (scissors), GDA ligation (linear stapler): ports *A* and *B* with surgeon on the right, fixed liver retractor through port *E*. (3) Mobilization of the ligament of Treitz: ports *A* and *B*. (4) Division of antrum (linear stapler): port *D* by first assistant on the left. (5) Pancreatic neck division (bipolar electrocautery with scissors at pancreatic duct), uncinate resection (bipolar electrocautery and clips): ports *A*, *B*, and *D*. (6) Specimen extraction: right lower quadrant 5-cm muscle-sparing incision (*F*) with wound protector. (7) Pancreaticojejunostomy (reconstructive limb brought behind the root of the mesentery to create a neoduodenum): ports *D* and *E* with a surgeon on the left, liver retractor removed. (8) Hepaticojejunostomy: ports *A* and *B* with surgeon back on the right, liver retractor replaced in port *E*. (9) Stapled gastrojejunostomy: ports *A* and *B* with surgeon on the right

transfusion, final pathological diagnosis, lymph node harvest (*n*), margin status (R0 versus R1), postoperative complications, hospital length of stay (days), administration of adjuvant therapy, and disease-specific and overall survival. Identical data from a group of 14 OPD patients were compared to the LPD cohort.

Statistical Analysis

Using the SPSS (Chicago, IL), data were imported and verified. Descriptive statistics were performed to characterize the sample. With the exception of tumor size and number of harvested lymph nodes, the data were non-normally distributed therefore nonparametric statistics were performed. Mann–Whitney *U* tests were used to test between group differences with continuous variables and chi-square analyses for categorical variables.

Results

Between September 2008 and March 2010, 14 patients underwent a planned LPD. A matched cohort of 14 OPD patients was treated between January 2006 and August 2008. The patient characteristics and operative data for both groups are presented in Table 1. With respect to overall health, 35.7% of the LPD patients were American College of Anesthesiology Score (ASA) class II, and 64.3% of the patients were ASA class III. The median LPD operative time was 456 min (range, 334–583 min; interquartile range (IQR), 109.5), and the median estimated blood loss (EBL) was 300 ml (range, 150–1,300 ml; IQR, 225). Immediate postoperative intensive care unit (ICU) care was deemed appropriate for five LPD patients (36%), and four patients received a perioperative (within 72 h) blood transfusion (29%). The LPD median ICU stay was 0 days and the median length of hospital stay was 8 days (range, 5–28 days; IQR, 8.5). When compared to the OPD group, only operative times were significantly different: LPD, 456 min (range, 334–583 min) and OPD 372.5 min (range, 290–628 min) (P=0.01).

The primary indication for LPD proved to be malignancy (12 out of 14, 88%). Table 2 summarizes the final pathological diagnoses. Initial patient selection intentionally attempted to exclude ductal adenocarcinoma of the pancreatic head, and of the eight cases of pancreatic cancer, four had preoperative clinical diagnoses of the distal bile duct or ampullary cancer. The other four cases represented subsequent cases and lacked any features by imaging of portal vein or celiac or superior mesenteric artery encroachment by the neoplasm. Table 3 summarizes stage, margin, and lymph node harvest data for both groups. Regarding the LPD cohort, an R0 resection margin was achieved in all 12 cases of malignancy. The average tumor size was smaller in the LPD group (LPD, 2.2 cm; range, 0.8–4.7 cm versus OPD, 3.6; range, 3–5 cm; p=0.02), and the mean number of retrieved lymph nodes was comparable: LPD, 18.5 (range, 12–31); OPD, 19.1 (range, 10–36) (p=0.85). The one T4N1 lesion in the LPD group was a duodenal adenocarcinoma with invasion of the pancreatic parenchyma and common bile.

The postoperative outcomes and complications are summarized in Table 4. No significant differences were noted with regard to postoperative morbidity between the two groups. A conversion to an open procedure was necessary in two cases (14%). Regarding these cases, the first patient with a BMI of 37 was converted due to failure to progress during exposure of the third portion of the duodenum. The second patient required conversion secondary to intraoperative bleeding from the portal vein in the setting of chronic pancreatitis (EBL, 1,300 ml); this patient subsequently required resectioning of a 2-cm segment of

Table 1 Patient, operative, and perioperative characteristics

Characteristic	Lap	Open	*P* value
Patient (no.)	14	14	
Age mean (SD)	69.8 (10.2)	67.4 (11)	0.56
Gender (male, %)	78.6	50	0.12
ASA, II/III (%)	35.7/64.3	50/50	0.45
BMI, median (IQR)	28.5 (4.9)	30.0 (4)	0.39
Operative time (median, min) (IQR)	456 (109.5)	372.5 (117.5)	0.01
Blood loss (median, mL) (IQR)	300 (225)	400 (750)	0.23
Patients transfused (no., %)	4 (28.6%)	5 (35.7%)	0.69
ICU stay (median, days)	0	0.5	0.98
Length of stay (median, days) (IQR)	8 (8.5)	8.5 (3)	0.71

Lap laparoscopy

the portal vein with primary reconstruction secondary to the poor quality of the tissues.

Within the LPD cohort, there was a single mortality that occurred 44 days postoperatively (grade V Clavien[12]) due to a multisystem organ failure secondary to sepsis (aspiration on POD 5 resulting in bilateral pneumonia). Three other LPD patients had a major complication (Clavien grade III or IV, necessitating radiological, endoscopic, or operative intervention and/or causing organ failure). These included gastric staple line bleeding necessitating reoperation (performed laparoscopically) on postoperative day 1 ($n=1$), pulmonary embolus and aspiration pneumonia requiring reintubation ($n=1$), and upper gastrointestinal hemorrhage from marginal ulcer 30 days postoperation requiring therapeutic gastroscopy ($n=1$).

Six LPD patients suffered a minor complication (Clavien grade I or II, not necessitating radiologic, endoscopic, or operative intervention and not causing organ failure). A detailed listing of these complications includes infection of the utility incision ($n=2$), delayed gastric emptying prolonging hospital stay ($n=2$), delayed gastric emptying and portal vein thrombosis ($n=1$), and wound infection and prolonged ileus necessitating TPN and antibiotics for 1 week ($n=1$). Finally, a pancreatic leak occurred in five LPD patients (36%). All leaks were grade A (ISGPF)[13] and were adequately controlled by the intraoperatively placed drains. These leaks were diagnosed by checking a drain amylase on the third postoperative day regardless of effluent character or volume. All of these leaks had been sealed and the drains removed within 5 weeks of the operative date.

Of the 12 LPD patients with malignancy, an adjuvant treatment was indicated in nine of the cases based upon histological diagnosis and stage. Five of the nine (55.5%) patients commenced adjuvant treatment with a mean time from surgery to onset of chemotherapy of 60 days (range, 41–80). The reasons for not commencing adjuvant chemotherapy included surgical mortality ($n=1$), poor postoperative functional status ($n=1$), patient refusal ($n=1$), and loss to follow-up ($n=1$). At median follow-up of 9.5 months (range, 4–21 months), only one patient has had a recurrence.

In Table 5, the operative details and outcomes between the first and last seven LPD cases are compared to ascertain evidence of a learning curve. Using the Mann–Whitney *U* and chi-square analyses, trends of reduced operative time, blood loss, and shorter hospitalization were observed, but these differences did not reach statistical significance. No significant differences in complication rates or pancreatic fistula rates were noted.

Table 2 Final histological diagnoses

Diagnosis	Lap ($N=14$)	Open ($N=14$)
Pancreatic adenocarcinoma	8	8
Cholangiocarcinoma	2	2
Duodenal adenocarcinoma	1	0
Duodenal GIST	1	1
Duodenal adenoma	0	2
IPMN	1	1[a]
Chronic pancreatitis	1	0

GIST gastrointestinal stromal tumor, *IPMN* intraductal papillary mucinous neoplasms, *Lap* laparoscopy

[a] IPMN with carcinoma in situ

Discussion

Given the potential of a reduced morbidity, we embarked on implementing LPD at a high-volume pancreatic surgery center. Our approach was cautious due to concerns that patient safety and operative outcomes could be compromised during the early experience. We aimed to meet the standards as published by Winter et al. who reported overall perioperative mortality and morbidity rates of 2% and 38%, respectively (1% and 45% in the last decade) including a

Table 3 Oncological data

Oncological Parameter	Lap, *N*=12	Open, *N*=12	*P* value
Tumor size (mean, cm)	2.2 (SD, 1.1)	3.6 (SD, 1.1)	0.02
Stage (AJCC sixth)[a]			0.88
CIS[b]	0	1	
T2N0M0	1	1	
T3N0M0	3	2	
T3N1M0	5	6	
T4N0M0	1	0	
T4N1M0	1	1	
Resection margin			
R0	12 (100%)	11 (91.7%)	0.31
R1/R2	0	1 (8.3%)	
Lymph node harvest (mean, *n*)	18.5 (SD, 6.2)	19.1 (SD, 8.3)	0.85

Lap laparoscopy

[a] Pancreatic and periampullary cancers

[b] Carcinoma in situ

reoperative rate of 3% and a median length of stay of 9 days (8 days in the last decade) in a series of 1,175 OPD performed for pancreatic cancer.[14]

Our results from a small series of patients did not quite meet this exceptional standard; however, our single mortality unrelated to surgical technique, a single reoperation, and the morbidity rate and median length of stay do compare favorably. This data suggests that a laparoscopic pancreaticoduodenectomy can be implemented in a high-volume pancreatic surgery center without subjecting patients to an unacceptably higher risk of complications early in the surgeon's experience. Our intraoperative and immediate oncological parameters such as blood loss, resection margin, and lymph node harvest are comparable to this and other large open series.[14,15] Thus, our results further suggest that LPD can be implemented without compromising oncologic principles of the procedure. We conclude that the learning curve of a surgeon embarking on the performance of LPD impacts the duration of the procedure, but does not negatively impact complication rates, margin status, lymph node harvest, blood loss, need for transfusion, or need for intensive care. Furthermore, the early operative experience does not necessarily equate with a high conversion rate as we were able to perform an LPD in 12 out of 14 patients successfully (86%).

Since Gagner's first report of LPD in 1994,[1,16] there have only been three series of patients undergoing LPD reported (Table 6).[2–4] It is unclear from these prior manuscripts how these centers embarked upon the performance of LPD, whether cases performed during their initial experience were excluded, or whether a disproportionate number of complications occurred early in their experience. Our data compares favorably with most of the outcomes reported in these prior studies, particularly with regard to immediate oncological surrogate markers, morbidity, and length of stay. Our overall pancreatic fistula rate (36%) is higher than that reported by

Table 4 Conversions, morbidity, and mortality

Complication		Open, *N* (%)	Lap, *N* (%)	Comment on laparoscopic patients
Conversion			2 (14%)	Portal vein bleed=1; failure to progress=1
Mortality		0	1 (7%)	Aspiration pneumonia
Reoperation		1 (7%)	1 (7%)	Gastric staple line bleed
Pancreatic fistula[a]		6 (42.8%)	5 (36%)	4 Leaks occurred in soft glands, <3 mm ducts
	Grade A	5	5	
	Grade B/C	1	0	
Clavien[b] I/II		5 (35.7%)	6 (42%)	Delyed gastric emptying=3; wound infection=3
Clavien[c] III/IV		1 (7.1%)	3 (20%)	Gastric staple bleed=1; PE=1, GJ ulcer bleed=1

All *P* values are not significant

Lap laparoscopy, *PE* pulmonary embolus, *GJ* gastrojejunostomy

[a] International Srudy Group for Pancreatic Fistula criteria

[b] Complications not requiring radiologic, endoscopic, or operative intervention and not causing organ failure

[c] Complications requiring radiologic, endoscopic, or operative intervention and not causing organ failure

Table 5 Comparison between early and late laparoscopic patients

Parameter	Cases 1–7	Cases 8–14	*P* value
Conversions (no.)	2	0	
Mortality (no.)	0	1	
Pancreatic fistula (no.)	2	3	
Clavien I–II complications (no.)[a]	3	3	
Clavien III–IV complications (no.)[b]	2	1	
Operative time (median, min)	474	445	0.14
Estimated blood loss (median, mL)	325	250	0.43
Length of stay (median, days)	9	7	0.22

[a] Complications not requiring radiologic, endoscopic, or operative intervention and not causing organ failure

[b] Complications requiring radiologic, endoscopic, or operative intervention and/or causing organ failure

others, but may represent differences in diagnosis criteria and patient selection bias that resulted in a high percentage of the patients in our series having normal, soft pancreata. Four of our five LPD leaks occurred in soft glands with small caliber ducts. None of these leaks was associated with a clinical event, nor did the pancreatic leak rate appear to be influenced by a learning curve.

One impetus for LPD is the hope it will result in a reduced postoperative morbidity, and thus the successful institution of adjuvant therapy will be an important endpoint to determine its superiority to OPD. The administration of chemotherapy has proven beneficial in pancreatic cancer patients,[17–19] but its delivery is limited to approximately 40–60% of surgical patients due to postoperative complications, prolonged convalescence, patterns of referral, and the location/nature of the treatment facility.[20,21] In this series, 55% of patients received adjuvant chemotherapy, and the average time to its institution was 60 days. A larger series and longer follow-up will be necessary to determine any benefit of LPD with respect to the successful initiation of adjuvant treatment, reduction in complication rates, or improvement in quality of life.

The impact of LPD on health care delivery costs is an important unanswered issue, but we did not perform a cost analysis on this early experience for a number of reasons. First, we observed a decrease in operative times with increasing experience, had not reached a nadir, and this is a major component of cost. Furthermore, this variable is dependent upon the individual surgeon, and the conclusions from a single surgeon's experience may not prove to be applicable to a population of surgeons. Finally, the length of stay for this cohort was artificially prolonged to ensure safe hospital discharge early in our experience. Future study in this regard is clearly warranted.

The philosophy regarding patient selection and the performance of LPD for malignancy early in a surgeons experience is not straightforward. The potential for a compromised dissection must be weighed against the ease of reconstruction. Thus, ampullary pathology leading to dilation of both the biliary and pancreatic ducts and pancreatic fibrosis without compromise of retroperitoneal or vascular margins may represent the ideal situation for initial attempts at LPD. Our R0 resection rate of 100% supports the use of our previously published preoperative predictive model of negative margin resection that employs findings of CT and EUS imaging.[10] Obese patients and patients with chronic calcific pancreatitis pose additional technical challenges that may be best avoided early in a surgeon's experience.

Finally, these results may not be generalized, and questions remain regarding what training and experience is best to prepare a surgeon to safely perform LPD. We anticipate that a number of experienced pancreatic surgeons will embark upon LPD in the near future. We found that the dissections and reconstructions on cadavers to be very

Table 6 Total laparoscopic pancreaticoduodenectomy series

Parameter	Dulucq[a]	Palavinelu[a]	Kendrick	Current
Year	2006	2009	2010	2010
Patient (no.)	13	75	65	14
Conversion (%)	NA	0	4.6	14
Mortality (no.)	1	1	1	1
Operative time (median, min)	295	357	368	456
Estimated blood loss (median, mL)	89	74	240	300
R0 resection (%)	100	97	89	100
Lymph node harvest (median, no.)	18	14	15	18.5
Pancreatic fistula (%)	8	7	18	36
Length of stay (median, days)	16	8	7	8

[a] Operative time, blood loss, lymph node harvest, and length of stay were reported as mean

helpful. The subsequent performance of our initial LPD with the intent of laparoscopic resection and open reconstruction helped us gain efficiency and confidence in the setting of intended conversion to an open procedure. In our opinion, familiarity with the anatomy, and technical assessment of the adequacy of the anastamoses were more important than minimally invasive surgical skill.

Conclusion

In summary, we have presented an early experience in performing total laparoscopic pancreaticoduodenectomy. Our results suggest safety and feasibility in the implementation of this procedure when performed at a high-volume tertiary care center by a surgical team experienced in open pancreatic and minimally invasive surgery. Early postoperative outcomes and oncologic surrogate results will not be compromised if appropriate surgical expertise is coupled to careful patient selection.

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ORIGINAL ARTICLE

Delayed Gastric Emptying after Pancreaticoduodenectomy: Influence of the Orthotopic Technique of Reconstruction and Intestinal Motilin Receptor Expression

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Abstract
Background Delayed gastric emptying (DGE) is still a common postoperative complication after pancreaticoduodenectomy (PD). Because different reconstruction techniques after PD and the influence of motilin receptor expression are controversially discussed, the present study analyzed the influence of a total orthotopic reconstruction technique on DGE after PD.
Methods Data from patients undergoing PD and reconstruction using a total orthotopic technique were reviewed, and correlations between DGE and clinico-pathological variables were analyzed. Motilin receptor expression was measured within the duodenum, jejunum, and terminal ileum.
Results Three hundred seven patients received orthotopic reconstruction using a single jejunal loop. DGE grade B or C could be observed in 16.6% of the patients. DGE was significantly associated with the severity of a postoperative pancreatic fistula, the need for a reoperation, wound infections, and vascular complications. Furthermore, these parameters correlated significantly with the grade of DGE. The density of motilin receptor expression decreased significantly behind the duodenum in aboral direction.
Conclusions The orthotopic reconstruction after PD is the shortest distance without resection of a jejunal segment, preserves the greatest length of jejunum and thus the highest density of motilin receptors, and should therefore be recommended to reduce the incidence of DGE after PD.

Keywords Pancreaticoduodenectomy · Reconstruction technique · Delayed gastric emptying · Motilin receptor

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Introduction

After the first description of a one-stage radical pancreaticoduodenectomy (PD) including the resection of the distal stomach and the pylorus,[1] its modification by Traverso and Longmire in 1978[2] with the preservation of the pylorus has become a standard procedure for various benign and malignant diseases of the pancreatic head, with low mortality rates in most high-volume centers.[3–7] Despite the improvement in mortality, postoperative morbidity still remains high (30–50%), mostly related to postoperative pancreatic fistula (POPF) formation and delayed gastric emptying (DGE) in the early postoperative course.[6–10]

Delayed gastric emptying is a common, yet self-limiting and non-fatal postoperative complication after PD with an incidence of 3–81% depending on the classification applied.[10–14] The etiology of DGE after PD is still

discussed controversially in the literature. Whereas several preoperative risk factors have been associated with postoperative DGE, direct influence of surgical complications on gastric emptying have been well-described, namely for septic and other intraabdominal complications.[4,7,15] Furthermore, regarding the influence on DGE, different reconstruction techniques for the gastrointestinal tract after PD like pylorus preservation or retrocolic/antecolic reconstruction exist.[4,16–20]

Resection of the duodenum and the proximal part of the jejunum results in decreased circulating motilin and might be one important etiological factor for DGE.[20–24] Interestingly, it has been shown that erythromycin, a motilin receptor agonist, initiates phase 3 activity of the gastric motor complex and significantly reduces the incidence of DGE after pylorus-preserving PD.[25,26] In the present study, we therefore analyzed the influence of a total orthotopic reconstruction using the first jejunal loop to preserve motilin receptor expression on DGE after PD.

Patients and Methods

Data from all patients undergoing pancreatic surgery were prospectively entered in an i.s.h. med database (GSD, Berlin, Germany) running on a SAP platform (SAP, St. Leon-Rot, Germany). For this study, data from patients undergoing pancreatic head resections between March 2001 and April 2008 were retrieved from the database and analyzed retrospectively.

Surgical Technique and Postoperative Care

All patients undergoing pancreatic head resection had a standardized general anesthesia including epidural analgesia, balanced volume status, and prophylactic perioperative antibiotics. PD was performed as partial pancreatectomy, i.e., resection of the head of the pancreas with or without pylorus preservation. Distal gastric resection was only performed for oncological reasons and when the postpyloric duodenum was infiltrated. The right gastric artery and the right gastroepiploic vessels were routinely dissected without resection of the major omentum. In all patients, reconstruction was performed using a total orthotopic technique as shown in Fig. 1: without resection of a jejunal segment the first jejunal loop was placed within the original duodenal bed behind the mesenteric vessels (Fig. 1a, b). The pancreaticojejunostomy was performed as a two-layer end-to-side anastomosis in duct-to-mucosa technique using PDS 6–0 (mucosa to pancreatic duct) and PDS 5–0 (sero-muscular onto the pancreatic capsule and parenchyma; Fig. 1c). A single-layer end-to-side hepaticojejunostomy was performed 10–15 cm distal to the pancreatojejunostomy using PDS 5–0. The duodenojejunostomy was achieved 30–35 cm distal to the hepaticojejunostomy using PDS 4–0 and 5–0 in dual-layer technique (Fig. 1d). Thus, only one jejunal loop was used for reconstruction. All three anastomoses were placed above the mesenteric vessels. No stents were used for pancreatic and biliary anastomoses. Patients with benign diseases received no specific lymphadenectomy, i.e., only the peripancreatic lymph nodes were excised en bloc with the resected specimen. In patients with malignancies, either a standard lymphadenectomy (excision of the lymph nodes 4d, 5, 6, 8a, 8p, 12a, 13, 14v, and 17 according to the Japanese lymph node classification)[27] or an extended lymphadenectomy (additional excision of the lymph nodes 9, 12b, 12p, 14a, and 16 according to the Japanese lymph node classification)[27] was performed. Two soft easy-flow drains were routinely placed behind and in front of the pancreatic anastomosis and the hepaticojejunostomy, respectively. Postoperatively, patients were transferred to the intensive care unit. Data were recorded prospectively in our database system including all demographic details, disease-related data, medical data, and data from the peri- and postoperative course.

All patients had routinely a nasogastric tube for decompression. Oral diet was initiated at the same postoperative day (POD) when the gastric tube could be removed. As different definitions of DGE exist in the literature, such as the inability to tolerate regular diet by the 14th POD or the inability to tolerate liquid diet after 7 days, we classified DGE retrospectively to grades A, B, or C according to the definition of the International Study Group of Pancreatic Surgery (ISGPS)[28] as shown in Table 1. Associations between DGE and clinical data concerning patient demographics, perioperative factors, and postoperative complications were studied by univariate analysis followed by a multivariate logistic regression model. POPF was defined according to the classification of the International Study Group on Pancreatic Fistula,[8] revised by Hashimoto et al.[28]

The shortest necessary length for different ways of reconstruction, i.e., the distance between the ligament of Treitz and the pancreatic corpus was analyzed in consecutive 25 patients intraoperatively in 2008. Within these 25 patients, the individual three distances for orthotopic, retrocolic, or antecolic technique of reconstruction were measured using a 5-mm mersilene band mimicking the jejunal segment.

Human Tissue Samples and Immunohistochemistry of the Motilin Receptor

Specimen of the duodenum (pars superior, pars descendens, and pars inferior) and the first part of the jejunum (4 or 40 cm after the ligament of Treitz, respectively) were collected from ten patients each undergoing PD without

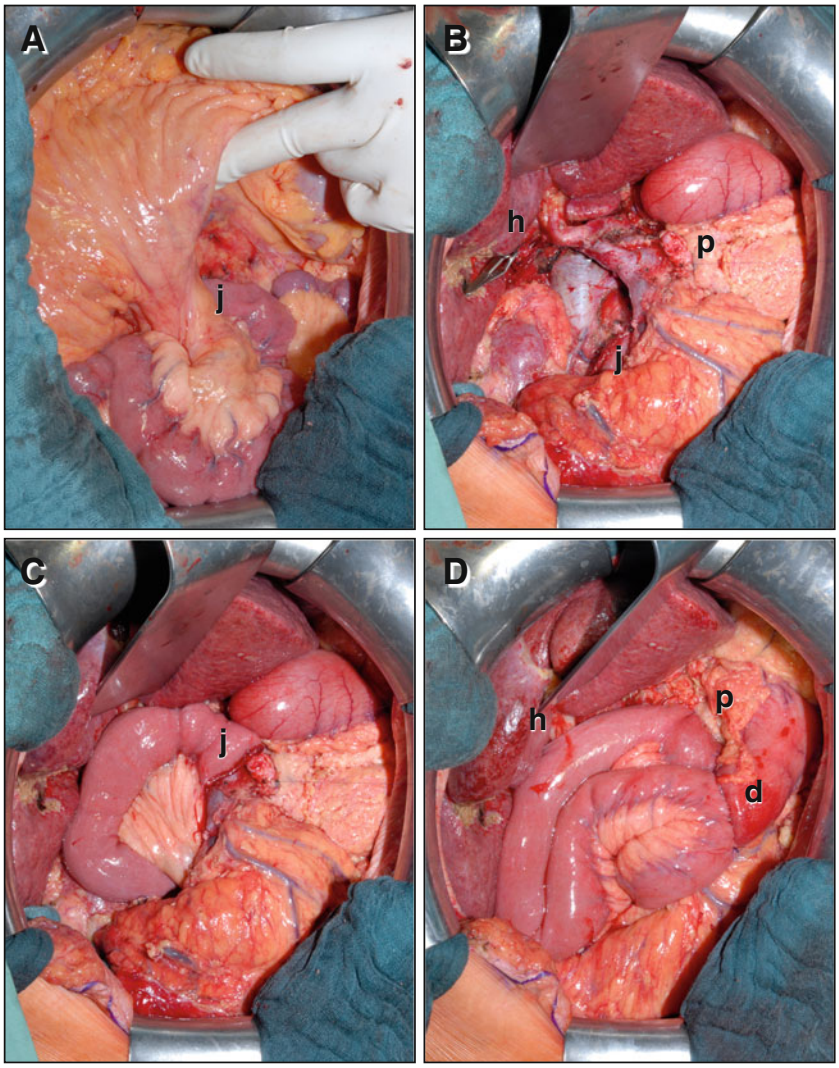

Fig. 1 Intraoperative photography of the orthotopic reconstruction technique after pylorus-preserving pancreaticoduodenectomy. **a** Inframesocolic view showing the first jejunal loop (*j*) within the original duodenal bed behind the mesenteric vessels. **b** supramesocolic view after resection of the pancreatic head (*p* resection margin of the pancreas, *h* common hepatic duct, *j* first jejunal loop), **c** placement of the first jejunal loop (*j*) within the original duodenal bed before anastomoses, **d** final view after completion of the pancreaticojejunostomy (*p*), hepaticojejunostomy (*h*), and duodenojejunostomy

orthotopic reconstruction. Additional specimens of the terminal ileum were collected from patients who underwent right hemicolectomy. All patients provided informed consent for tissue procurement, which was approved by the local ethics committee. Tissue samples were snapped frozen and stored at −80°C.

To study motilin receptor-positive cells, cryostat tissue sections were stained using indirect immunoperoxidase techniques. Sections were incubated with a goat antihuman GPR38-A polyclonal antibody (Santa Cruz, Heidelberg, Germany) followed by incubation with a biotinylated rabbit anti-goat antibody (DakoCytomation, Hamburg, Germany) and peroxidase-labeled streptavidin (DakoCytomation). Sections were stained by incubation in 0.1 M acetate buffer (pH 5.2) containing 0.03% 3-amino-9-ethylcarbazole and 0.03% H_2O_2, resulting in a red staining. Finally, sections were counter-stained with hemalaun according to Mayer and examined by light microscopy. For quantitative analysis, the number of motilin receptor-positive cells within the duodenum, jejunum, and ileum was counted in 20 high-power fields.

Table 1 Definition of delayed gastric emptying (DGE) according to the International Study Group of Pancreatic Surgery (ISGPS) modified by Hashimoto Y et al.[28]

DGE grade	No DGE	Grade A	Grade B	Grade C
Gastric tube removed on POD	≤3	4–7	8–14	≥15
Gastric tube reinserted anytime after POD	None	>3	>7	>14
Unable to tolerate solid oral diet by POD	–	7–13	14–20	≥21

POD postoperative day

Statistical Analysis

Data are expressed as absolute numbers or mean± standard error of the mean (SEM) unless indicated otherwise. Differences between the two study groups were calculated as followed: categorical variables were analyzed by chi-square test or Fisher's exact test, whereas continuous variables were analyzed by Mann–Whitney test or Kruskal–Wallis test, as appropriate. Differences between more than two groups (Table 4) were calculated by ANOVA followed by the recommended post hoc test. Overall statistical significance was set at $p<0.05$. Multivariate analysis was performed using a binary logistic regression model expressed in odds ratio. The 95% confidential intervals are shown with upper and lower limit. To test the independence of the risk and associated factors for DGE, significant variables ($p<0.15$) in the univariate analysis were entered into a multivariate logistic regression model. Statistical analysis was performed with the use of the software package SPSS 14.0® (SPSS GmbH Software, Munich, Germany).

Results

Between March 2001 and April 2008, 327 out of 700 patients admitted for pancreatic surgery underwent PD. While 20 out of these 327 patients received a single or double retrocolic jejunal loop in Roux-Y technique for reconstruction due to anatomical or oncological reasons, reconstruction after PD using the total orthotopic technique with a single jejunal loop could be performed in 307 patients. These 307 patients were included within the present study.

There were 176 male (57.3%) and 131 female (46.7%) patients with a mean age of 63.2±0.7 years at the time of pancreatic surgery (Table 2). Forty percent of the patients had prior abdominal operations. The ASA score was two in 58% and three in 38.4% of the patients. All patients had elective operations after a complete preoperative workup. Indications for PD (Table 2) were malignant disorders, mostly pancreatic head carcinoma ($n=117$) and benign disorders like chronic pancreatitis ($n=72$). Indications for the operation and histological characteristics showed no statistical differences comparing patients with or without postoperative DGE (Table 3). Out of the 307 patients undergoing PD, postoperative DGE grades A, B, or C could be observed in 130 patients. According to patients' demographics and characteristics, no statistical differences could be observed comparing patients with or without postoperative DGE (Table 3).

Surgical procedures are listed in Table 2. In 89.3% of the patients, a pylorus-preserving PD was performed, whereas in 10.7% of the patients, an additional distal gastrectomy was necessary. Pylorus preservation had no influence on the occurrence of postoperative DGE (Table 3). One hundred and fifty-five out of the 307 patients underwent extended lymphadenectomy without correlation to DGE. The operative time was longer, which approached statistical significance ($p=0.079$), and the blood loss was similar ($p=0.256$) in patients with postoperative DGE compared to patients without DGE.

Analyzing the shortest necessary length for reconstruction revealed that the distance for orthotopic reconstruction was 11±0.6 cm (Table 4). Compared with the retrocolic (14±1 cm) and antecolic (21±1 cm) technique of reconstruction, this distance was significantly shorter. Furthermore, due to the shortness of the mesenterium of the first jejunal loop—for a retro- or antecolic Roux-Y reconstruction resection up to 40 cm of the jejunum is

Table 2 Demographics ($n=307$), indications, histological characteristics, and operative details of 307 patients undergoing pancreaticoduodenectomy with a total orthotopic technique of reconstruction

Parameters	Total ($n=307$)
Gender [female/male]	131/176
Age [years]	63.2±0.7
Age >65 years	154 (50.2%)
ASA score	
I	6 (2.0%)
II	178 (58.0%)
III	118 (38.4%)
IV	5 (1.6%)
Diabetes mellitus	91 (29.6%)
Smoking	96 (31.3%)
Chronic alcoholism	52 (16.9%)
Previous abdominal operation	123 (40.1%)
Pancreatic cancer	117 (38.1%)
Malign tumor of the papilla vateri	32 (10.4%)
Duodenal cancer	10 (3.3%)
Distal bile duct cancer	28 (9.1%)
Other malignant tumors	16 (5.2%)
Benign pancreatic tumors	32 (10.4%)
Chronic pancreatitis	72 (23.5%)
Pylorus-preserving PD	274 (89.3%)
PD with distal gastrectomy	33 (10.7%)
Portal vein resection/reconstruction	44 (14.3%)
No specific lymphadenectomy	105 (34.2%)
Standard lymphadenectomy	47 (15.3%)
Extended lymphadenectomy	155 (50.5%)
OR time (h:min)	4:59±0:04
Blood loss (ml)	618±34

Mean±SEM or *n* (%)

ASA American Society of Anesthesiologists

Table 3 Demographics, histological characteristics, and operative details of 307 patients undergoing pancreaticoduodenectomy with orthotopic reconstruction. Patients suffering from postoperative delayed gastric emptying (DGE) grades A to C were compared to patients without (no DGE)

Parameters	No DGE (n=177)	DGE (n=130)
Gender [female/male]	75/102	56/74
Age [years]	61.8±0.9	64.9±0.9
Age >65 years	80 (45.2%)	74 (56.9%)
ASA score		
I	4 (2.3%)	2 (1.5%)
II	106 (59.9%)	72 (55.4%)
III	66 (37.3%)	52 (40.0%)
IV	1 (0.5%)	4 (3.1%)
Diabetes mellitus	58 (32.8%)	33 (25.4%)
Smoking	58 (32.8%)	38 (29.2%)
Chronic alcoholism	36 (20.3%)	16 (12.3%)
Previous abdominal operation	65 (36.7%)	58 (44.6%)
Pancreatic cancer	71 (40.1%)	46 (35.4%)
Malign tumor of the papilla vateri	21 (11.9%)	11 (8.5%)
Duodenal cancer	5 (2.8%)	5 (3.8%)
Distal bile duct cancer	17 (9.6%)	11 (8.5%)
Other malignant tumors	8 (4.5%)	8 (6.2%)
Benign pancreatic tumors	15 (8.5%)	17 (13.1%)
Chronic pancreatitis	40 (22.6%)	32 (24.5%)
Pylorus-preserving PD	161 (90.9%)	113 (86.9%)
PD with distal gastrectomy	16 (9.1%)	17 (13.1%)
Portal vein resection/reconstruction	28 (15.8%)	16 (12.3%)
No lymphadenectomy	58 (32.8%)	47 (36.1%)
Standard lymphadenectomy	27 (15.3%)	20 (15.4%)
Extended lymphadenectomy	92 (51.9%)	63 (48.5%)
OR time (h:min)	4:51±0:05	5:10±0:07
Blood loss (ml)	599±47	643±48

Mean±SEM or n (%); no statistical difference could be observed comparing both groups

ASA American Society of Anesthesiologists

necessary—the total orthotopic technique of reconstruction can be performed without resection of a jejunal segment.

Because DGE is often related to postoperative complications, intra- and postoperative morbidity and in-hospital mortality of the 307 patients were analyzed according to whether the patients presented with DGE or not (Table 5). Additionally, these parameters were correlated to the grade of DGE (Table 6). As shown in Table 5, 130 out of 307 patients (42.3%) developed postoperative DGE. Patients with DGE mostly presented with grade A (n=79; 25.7%), whereas DGE grade B occurred in 34 patients (11.1%) and 17 patient had DGE grade C (5.5%; Table 6). The mortality rate was significantly higher in patients with DGE (13.1%; Table 5) and correlates with the grade of DGE (Table 6). Whereas patients with DGE grade A had a comparable mortality rate to patients without DGE (3.8% vs. 3.4%), mortality was significantly (p<0.001) associated with DGE grades B (23.5%) and C (35.3%). The occurrence of a POPF (types A–C), the need for reoperations and secondary abdominal wall closure were significantly higher in the group of patients with DGE (Table 5). Reasons for reoperations were arterial complications (n=16), bile leakage (n=5), wound infection (n=8), intestinal ischemia (n=6), and fistula/abscesses (n=3). Furthermore, POPF and the need for reoperations were associated with DGE grades B/C (p=0.012 and p<0.001, respectively) and secondary closure of the abdominal wall with DGE grade C (p<0.001; Table 6). Interestingly, wound infections were significantly more associated with DGE grade C (p=0.015; Table 6).

Vascular complications like erosion bleeding and thrombosis of visceral vessels were associated with DGE grades B/C (Table 6). Cardiac complications were observed more often in patients with DGE (Table 5), and pulmonary complications (infection, embolism) were associated with

Table 4 Distance from the ligament of Treitz to the pancreatic corpus after partial pancreaticoduodenectomy (n=25); p value versus orthotopic technique of reconstruction

Technique of reconstruction	Distance (cm)	p value
Orthotopic	11±0.6	
Retrocolic	14±0	p<0.05
Antecolic	21±1	p<0.05

Table 5 Mortality and morbidity of 307 patients undergoing pancreaticoduodenectomy with orthotopic reconstruction

Parameters	Total n=307	No DGE n=177	DGE n=130	p value
Mortality	7.5%	3.4%	13.1%	$p<0.001$
POPF	29.0%	21.5%	39.2%	$p<0.001$
Reoperation	12.4%	6.2%	20.8%	$p<0.001$
Secondary abdominal wall closure	4.9%	2.3%	8.5%	$p<0.001$
Intraabdominal abscess formation	13.4%	10.7%	16.9%	$p=0.080$
Wound infection	9.8%	9.6%	10%	$p=0.908$
Vascular complications	5.2%	3.4%	7.7%	$p=0.094$
Urinary tract infection	7.2%	5.6%	9.2%	$p=0.240$
Pulmonary complication	16.6%	6.8%	30%	$p<0.001$
Cardiac complication	15.3%	11.9%	20%	$p<0.05$
Blood transfusions (units)	3.9±3.4	1.5±0.1	2.1±0.2	$p<0.001$
ICU stay (days)	4.9±0.4	2.7±0.1	7.8±0.9	$p<0.001$
Postoperative hospital stay (days)	19.2±0.8	15.4±0.5	24.3±1.6	$p<0.001$

Risk factors for postoperative delayed gastric emptying (DGE) were analyzed according to whether DGE (130 patients) occurred or not (177 patients). Complications are given in percentages of the group. Mean±SEM

DGE grades B/C (Table 6). Patients with DGE required more intra- and postoperative blood transfusions ($p<0.001$; Table 5), which was significantly associated with DGE grade C (Table 6). Accordingly, due to the complicated postoperative course, patients with DGE had a significantly longer stay in the ICU as well as a prolonged total postoperative hospital stay (Table 5), both significantly associated with the grade of DGE (Table 6).

Motilin receptor-positive cells could be observed within the submucosa of the duodenum and small intestine (jejunum) as shown in Fig. 2. Whereas sections from the terminal ileum showed only single motilin receptor-positive cells, the highest amount of motilin receptor-positive cells could be observed within the duodenum (pars superior, pars descendens, and pars inferior). The rate of motilin receptor-positive cells decreased significantly behind the duodenum in aboral direction. Whereas within the first 4 cm of the jejunum, the number of motilin receptor-positive cells was comparable to the duodenum, already 40 cm behind the ligament of Treitz, the number of motilin receptor-positive cells decreased significantly (Fig. 2).

Discussion

The major findings of the presented study are that the severity of DGE directly correlates with intra- and postoperative complications. The orthotopic technique of reconstruction, as described in the current study, may present a reasonable surgical concept to overcome the problem of DGE.

DGE is a leading cause of morbidity after PD but appears to be a short-term problem for most affected patients.[6–10] According to the literature, the incidence of DGE after pancreatic surgery still remains high. After PD with or without pylorus preservation, DGE is specified in

Table 6 Mortality and morbidity of 130 patients with postoperative delayed gastric emptying (DGE) after pancreaticoduodenectomy with orthotopic reconstruction

Parameters	DGE n=130	Grade A n=79	Grade B n=34	Grade C n=17	p value
Mortality	13.1%	3.8%	23.5%	35.3%	$p<0.001$
POPF	39.2%	29.1%	52.9%	58.9%	$p=0.012$
Reoperation	20.8%	5.1%	35.3%	64.7%	$p<0.001$
Secondary abdominal wall closure	8.5%	3.8%	5.9%	35.3%	$p<0.001$
Intraabdominal abscess formation	16.9%	12.7%	26.5%	17.6%	$p=0.101$
Wound infection	10%	6.3%	8.8%	29.4%	$p=0.015$
Vascular complications	7.7%	1.3%	14.7%	23.5%	$p=0.002$
Urinary tract infection	9.2%	7.6%	5.9%	23.5%	$p=0.088$
Pulmonary complication	30%	16.4%	44.1%	64.7%	$p<0.001$
Cardiac complication	20%	13.9%	26.5%	35.3%	$p=0.074$
Blood transfusions (units)	2.1±0.2	1.7±0.2	2.1±0.7	6.6±2.1	$p<0.001$
ICU stay (days)	7.8±0.9	4.2±0.5	8.5±1.4	23.1±4.4	$p<0.001$
Postoperative hospital stay (days)	24.3±1.6	18.9±1.5	26.9±3.1	44.4±6.4	$p<0.001$

Risk factors for DGE were compared to the grade (A to C) of DGE. Complications are given in percentages of the group. Mean±SEM

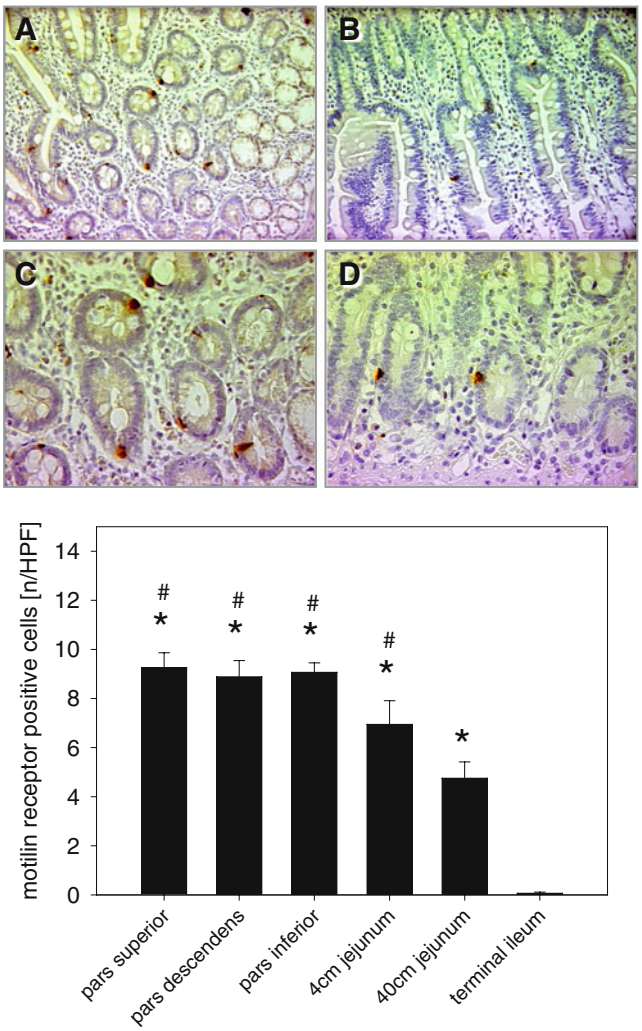

Fig. 2 Immunohistochemistry of motilin receptor-positive cells within the duodenum (**a**, **c**) and jejunum 4 cm as well as 40 cm behind the ligament of Treitz (**b**, **d**) of patients undergoing pancreaticoduodenectomy. Note that the number of motilin receptor-positive cells decreases significantly behind the ligament of Treitz. Mean±SEM; $*p<0.05$ vs. terminal ileum; $^{\#}p<0.05$ vs. 40 cm jejunum; original magnifications in **a** and **b** ×80, in **c** and **d** ×175

the literature within a range of 3–81% (Table 7). Within these studies, only clinically relevant DGE was documented and various definitions of DGE were used. For instance, Balcom et al. defined DGE as the failure to maintain oral intake by postoperative day 14,[5] a mixture of grades B and C DGE according to the ISGPS criteria.[14] This inconsistency confounds the ability to compare complication rates and outcome of new operative approaches as well as operative techniques and clinical trials. As shown in Table 7, all authors presented their rate of clinical relevant DGE after PD as a summation of grades B and C, with various definitions published until 2008 (Table 7). Using the ISGPS criteria for DGE, new studies present DGE grades B and C. Our study showed an incidence of clinically relevant DGE grades B and C of 11.1% and 5.5%, respectively. This low DGE rate is in line with newer literature, e.g., Hashimoto et al., reporting an overall DGE rate of 59% in 507 patients after PD,[28] but with a clinical relevant DGE rate (grades B and C) of only 12%. DGE grade C is a serious complication with a potential delay of adjuvant therapy. The findings of our own study with a very low rate of DGE grade C (5.5%) strongly suggest that the described operative approach with the total orthotopic technique of reconstruction using the first jejunal loop through the original duodenal bed may be reasonable to diminish the rate of DGE after PD.

Interestingly, whereas DGE could only be seen in 3% of the patients with no postoperative complications other than DGE after pylorus-preserving PD,[29] the pathogenesis of DGE has been speculated to involve several factors.

First, DGE is associated with preoperative risk factors. As shown by our own group, analyzing the prophylactic use of octreotide after PD to prevent pancreatic fistula in a prospective randomized double-blinded placebo-controlled trial, patients with a preoperative drainage of the bile duct subsequently have a lower rate of DGE than those without drainage.[13] Others have seen cholangitis,[12] age,[4] pancreatic fibrosis,[30] diabetes mellitus,[31] and malnutrition[31] as preoperative risk factors for DGE after pancreaticoduodenectomy. Furthermore, gastric dysrhythmia or atony results secondarily from intraabdominal complications such as POPF or abscesses.[4,7,15,28] DGE itself could be considered as a warning signal for intraabdominal complications, because in a recent study, postoperative DGE was strongly associated with intraabdominal complications like bleeding or infections requiring reoperation and the grade of POPF.[4,7] Interestingly, the present study shows for the first time that the severity (grades A to C) of DGE directly correlates with intra- and postoperative complications. The analyses showed that postoperative mortality, POPF, the rate of reoperations, wound infections, vascular complications, pulmonary failure, as well as the amount of blood transfusions directly correlate with the degree of DGE, especially in patients with grade C. Patients with DGE grade A had similar rates of intra- and postoperative complications than those without DGE after PD.

Second, it has been speculated that gastric atony and/or ischemic injury to the antropyloric muscle after resection of the duodenal pacemaker and disruption of the gastroduodenal neural connections leads to DGE after PD.[32] Reports from the literature are discordant. Whereas some authors showed that DGE is a disadvantage of pylorus-preserving PD compared with the classic Whipple procedure (PD),[19,20,33] others present a reduced[34] or a similar[35] DGE rate after pylorus-preserving PD compared to a classic Whipple operation (Table 7) and an earlier removal of the nasogastric tube.

Table 7 Overview of the literature comparing different resection/reconstruction techniques after pancreaticoduodenectomy (PD, ppPD=pylorus-preserving pancreaticoduodenectomy) regarding postoperative delayed gastric emptying (DGE)

	Number	Years	Study (patients)	DGE [%]
Yeo et al.[25]	118	1990–1993	PD (18) and ppPD (100): control (60) vs. erythromycin (58) treatment	30 vs. 19
Patel et al.[40]	67	1988–1994	PD (52) vs. ppPD (15)	41 vs. 61
van Berge Henegouwen et al.[20]	200	1989–1996	PD (100) vs. ppPD (100)	34 vs. 37
Fabre et al.[41]	88	1991–1997	PD	41
Horstmann et al.[19]	51	1994–1997	ppPD: antecolic duodenojejunostomy	12
Jimenez et al.[42]	72	1991–1997	PD (33) vs. ppPD (39)	12 vs. 33
Goei et al.[16]	174	1988–1998	ppPD: B I- (51) vs. B II-type (123) reconstruction	76 vs. 32
Balcom et al.[5]	489	1990–2000	PD (378) and ppPD (111)	12
Büchler et al.[6]	468	1993–2001	PD	23
Tran et al.[35]	170	1992–2000	PD (83) vs. ppPD (87)	23 vs. 22
Bassi et al.[17]	151	2002–2004	PD/pppD: pancreaticogastrostomy vs. -jejunostomy	3 vs. 12
Tani et al.[43]	40	2002–2004	ppPD: antecolic vs. retrocolic duodenojejunostomy	5 vs. 50
Niedergethmann et al.[34]	239	1994–2001	PD (128) vs. ppPD (111)	13 vs. 6
Reid-Lombardo et al.[44]	1,507	2000–2006	PD (336), ppPD (1075)—ISGPF vs. Saar criteria	13 vs. 14
Murakami et al. 2008[45]	132	1994–2006	ppPD retrocolic B I- (54) vs. antecolic Roux-en Y (78)	81 vs. 10
Nikfarjam et al. 2009[46]	151	2002–2008	PD/ppPD: antecolic vs. retrocolic gastro-/duodenojejunostomy	15 vs. 40
Parks et al.[47]	126	2002–2007	PD	21
Hashimoto et al.[28]	507	1988–2008	PD	12
Present study	307	2001–2008	ppPD with total orthotopic reconstruction	16.6

Only studies defining DGE, all authors defined DGE as clinically relevant DGE (grade B/C), were included in the analysis

Third, gastric atony after PD could occur in response to the reduction of circulating levels of motilin,[11,20,24] a hormone preliminary localized in the mucosa of the duodenum and proximal small intestine.[32,36,37] This point is of major interest, because our study shows for the first time that the density of motilin receptor-positive cells decreases significantly behind the duodenum in aboral direction. Motilin is responsible for stimulating the gastrointestinal motor complex. Consequently, the decrease of circulating motilin as well as motilin receptor-positive cells leads to a higher risk for developing gastric stasis after duodenal resection.[21,22,32] This association was confirmed in an animal model analyzing phase III pyloric motility in dogs undergoing pylorus-preserved PD.[38] Furthermore, it has been shown that erythromycin, a motilin receptor agonist that initiates phase 3 activity of the gastric motor complex,[11] significantly reduces the incidence of DGE.[25,26,39]

In this context, due to the important function of motilin for stimulation of the gastrointestinal tract, an obvious solution to reduce DGE after PD is to preserve the jejunum as much as possible. Consequently, a higher number of motilin receptors—as it is the case when preserving large parts of the proximal jejunum—should improve gastrointestinal motility after PD and therefore reduce the occurrence of DGE. Due to the fact that for a retro- or antecolic Roux-Y reconstruction resection of up to 40 cm of the jejunum is necessary, the total orthotopic reconstruction using the first draining jejunal loop without resection of a jejunal segment, as described herein for the first time, preserves the greatest length of jejunum and thus the highest density of motilin receptors. This statement is strengthened by our own findings that already 40 cm after the ligament of Treitz, the number of motilin receptor-positive cells decreases significantly.

Sometimes, patients after pancreaticoduodenectomy—especially those with benign disease—require endoscopic retrograde cholangiopancreatography due to stenosis of the bile duct anastomosis or bleeding of the pancreaticojejunostomy. Due to the short distance between the three anastomoses, our orthotopic technique enables an easy access for endoscopic interventions even years after surgery. To our best knowledge and experience, i.e., reoperations of patients with pancreatic cancer, tumor recurrence appears either locally, with peritoneal carcinosis or distant metastasis; however, the orthotopic reconstruction could not be accused for the symptoms of the patients.

A shortcoming of our study is the fact that there is no control group of patients being operated in a different manner than the orthotopic technique of reconstruction. Therefore, comparison of our own patients can only be performed with the known data from the literature (Table 7). Although DGE after PD has probably multi-factorial reasons, we would like to conclude that the total orthotopic

technique of reconstruction may be relevant for reduction of postoperative DGE. As other centers also report about low DGE rates of <20% (grades B and C) without analyses of their reconstruction technique and standardization, further studies should include the extent of the resected jejunal part and exact reports about the reconstruction technique to achieve better comparability. To compare all relevant parameters, the occurrence of DGE after PD would preferably necessitate a prospective randomized study, including different reconstruction techniques. Furthermore, data on the amount of the motilin receptor density at the site of the anastomosis of the jejunum with the pancreas could be of interest to identify risk factors for DGE after PD. The extent of the jejunal resection and the reconstruction technique should be performed identically to provide evidence for antecolic versus retrocolic reconstruction, reconstruction using the BI technique versus the Roux-Y technique, or a pancreaticojejunostomy of pancreaticogastostomy in order to improve the outcome of patients after PD.

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2010 SSAT POSTER PRESENTATION

Use of Intraoperative Ablation as an Adjunct to Surgical Resection in the Treatment of Recurrent Colorectal Liver Metastases

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Abstract
Objective To evaluate the role of intraoperative ablation as an adjunct to resection in patients with recurrent colorectal liver metastases (rCLM).
Methods All patients undergoing curative-intent reoperative surgery for rCLM from 1992 to 2009 at a tertiary cancer center were included. Overall survival (OS) and recurrence-free survival (RFS) were compared between patients treated with resection alone or in combination with ablation.
Results A total of 112 reoperative hepatectomies were performed, of which 16 were combined with ablation. The proportion of patients treated with resection and ablation increased from 0% to 41%. Patients undergoing resection and ablation had a greater tumor burden (median, 4 vs. 1, $p<0.0001$) and higher baseline clinical risk scores (median, 3 vs. 2, $p=0.065$) than patients undergoing resection alone. Patients undergoing resection and ablation had lower intraoperative blood loss than patients undergoing resection alone (344 vs. 877 ml, $p=0.018$). Five-year OS from the time of surgery was 48.6%. In multivariable analysis, there was no significant difference in OS or RFS based on the treatment modality.
Conclusion In patients with rCLM, the use of intraoperative ablation can extend the limits of surgical resection in patients with disease that might otherwise not be amenable to complete resection.

Keywords Colorectal cancer · Liver metastases · Ablation · Surgery

Introduction

The liver is the most common site of distant metastases from colorectal cancer with approximately 50% of colorectal patients developing liver metastases during the course of their disease.[1] Currently, surgical therapy offers the greatest likelihood of cure with a 10-year actual disease-specific survival rate of 17–25%.[2,3] However, despite complete resection, more than 75% of patients develop recurrence, with the liver remnant being a common site. Although many previous series have shown that repeat liver resection can be performed safely and effectively,[4–15] achieving a complete surgical resection (R0) in these settings is often technically difficult and in some cases impossible.

Recently, non-resectional ablative techniques have been developed, including radiofrequency ablation (RFA), cryoablation, and microwave ablation. These techniques, while safe, may be associated with worse oncologic outcomes, more so when performed percutaneously than intraoperatively.[16–21] Despite the potential disadvantages, ablative techniques can theoretically extend the limits of surgical resection by being performed in settings where R0 resection may be technically unfeasible or in patients with livers diseased from the use of chemotherapy where the morbidity of surgical resection is increased.[22–24] These situations are particularly relevant in the case of reoperative surgery for recurrent disease. In this study, we examined the role of

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intraoperative ablation as an adjunct to resection in the treatment of recurrent colorectal liver metastases (rCLM).

Methods

Study Design and Population

We conducted a retrospective cohort study using a prospectively collected institutional database maintained at Memorial Sloan-Kettering Cancer Center. The study population of 114 patients included all those who underwent curative reoperative surgery for rCLM from 1992 through 2009. Of these, a total of nine patients who underwent potentially curative surgery were excluded because of persistent disease present on the first postoperative cross-sectional imaging study. The study was approved by the Institutional Review Board.

Intervention

A previously reported standardized approach to hepatic resection was used in all cases.[25] This involved the use of low central venous pressure, appropriate vascular control, and parenchymal transection using the clamp-crush technique under intermittent Pringle control. Intraoperative ablation was performed using RFA, cryoablation, or microwave ablation. RFA was performed using the RITA system (Covidien, Burlington, MA). For the purposes of ablation, tumors were localized and the progress of ablation followed by intraoperative ultrasound with the aim of ablating a 1-cm margin around the tumor.

Statistical Methods

The primary outcome was overall survival (OS). Secondary outcomes included perioperative outcomes (complications, intraoperative blood loss, and operative time) and recurrence-free survival (RFS). RFS was measured from the date of each reoperation, and OS was measured in two ways—from the date of initial reoperation and the date of each reoperation. The type of surgical treatment—surgical resection alone (RES) or in combination with ablation (COMB)—was the primary independent variable. Covariates assessed included patient factors (age, sex) and tumor factors (number of tumors, size of tumors, clinical risk score,[3] disease-free interval). Complications were prospectively entered into the database and were graded on a scale of 1 to 5 according to a previously published grading system.[26] Grades 3 to 5 were classified as major complications.

Patient characteristics and outcomes were compared between groups using the t test or the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables. Survival outcomes were compared using Kaplan–Meier methods for univariate comparison and Cox proportional hazards for multivariable analysis. As the COMB group only comprised patients with multiple liver metastases, multivariable-adjusted survival outcomes were compared between three groups—resection of a solitary metastasis (RES1), resection of multiple metastases (RES2), and combination resection plus ablation of multiple metastases (COMB). All statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary NC). A two-sided p value<0.05 was considered to be statistically significant.

Results

Patient Characteristics

Over the study period, 105 patients with rCLM were identified. A total of 112 operations were performed for recurrent liver metastases in this cohort. Intraoperative ablation was used in 7/105 primary liver resections (6.7%) and in 16/112 (14.3%) repeat liver resections (COMB group). In the RES group, 72 of the 96 patients had a solitary liver metastasis (RES1), while 24 had multiple metastases (RES2). Patient and tumor characteristics of the groups are shown in Table 1. With respect to

Table 1 Baseline patient characteristics

	RES1 (n=72)	RES1 (n=24)	COMB (n=16)	p Value
Age (median, years)	62.5	58	58	0.91
Gender (% male)	51%	54%	88%	0.029
Clinical risk score (median)	2	2	3	0.078
Number of metastases (median)	1	3	3.5	<0.0001
Proportion with >1 metastasis (%)	0%	100%	100%	<0.0001
Largest metastasis (mean, cm)	3.1	4.1	2.7	0.04
Estimated blood loss (mean, ml)	852	954	344	0.013
Procedure time (mean, min)	215	266	266	0.048
Adjuvant chemotherapy (%)[a]	75.4%	84.2%	93.8%	0.23

Sample sizes under the column headings refer to number of operations (some patients had repeat operations)

[a] Chemotherapy after liver resection

patient characteristics, the groups were similar in age but a higher proportion of males was seen in the COMB group compared with the RES group. Among tumor factors, patients in the COMB group had a higher number of metastatic foci in the liver and slightly small tumors compared to patients in the RES group, with a trend toward higher baseline clinical risk score. There was no difference in the number of liver lesions (p=0.9) or the average clinical risk score (p=0.34) between the COMB and RES2 groups. In the COMB group, a median of 2 lesions were ablated.

Temporal Trends

There was a marked and steady increase in the use of intraoperative ablation over time from 0% in 1992–1997 to 41% in the 2007–2009 period (Fig. 1). In 84 cases, characteristics of the uninvolved liver parenchyma were documented and available for review. An increase over time was also seen in the proportion of patients undergoing surgery with abnormal liver parenchyma (steatosis, fibrosis, or inflammation) from 46% (1992–2000) to 61% (2001–2009).

Perioperative Outcomes

During reoperative surgeries, there was no significant difference in operative time between the two groups (COMB: 266 min vs. RES: 227 min, p=0.17). There was a significantly lower volume of estimated blood loss in the COMB group (344 vs. 877 ml, p=0.037). From 2001, when complications were captured prospectively, 16/66 patients (24.2%) experienced a complication within 60 days of surgery. Of these, five patients (10.6%) experienced a major complication (grade 3 or higher). There was no significant difference in the overall or major complication rate between the COMB and RES groups (COMB 12.5%, RES 28.0%, p=0.32). There were two early deaths in the RES group and none in the COMB group—one death was secondary to sequelae from postoperative hemorrhage and the other was from liver failure 100 days after surgery.

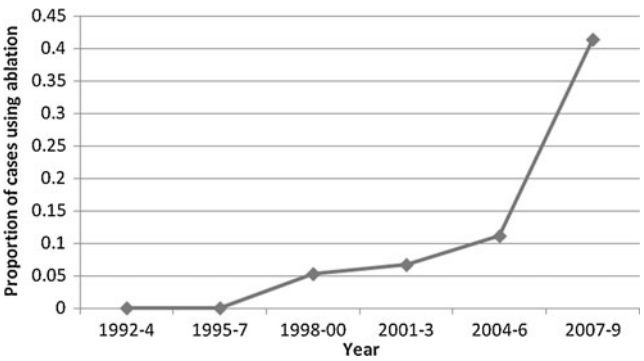

Fig. 1 Use of ablation over time

Oncologic Outcomes

The median follow-up among survivors from the time of first liver recurrence was 43 months, with an actuarial 5-year liver RFS of 39.6%, as measured from the time of surgery. There was a significant difference in RFS between the COMB and RES groups, with a median RFS of 38 months in the RES group compared with 14 months in the COMB group (p=0.012). RFS was also significantly associated with the number of liver metastases (median survival, 14 vs. 58 months, respectively, p=0.0002), and trends toward significance were noted with clinical risk score (p=0.15) and use of adjuvant chemotherapy (p=0.13). There was no significant difference between the COMB (resection and ablation of multiple metastases) and RES2 (resection-only of multiple metastases) groups with a median survival of 14 months in both groups (p=0.78) (Fig. 2). In multivariable analysis, there was no significant difference in risk of recurrence between the COMB and RES2 groups (hazard ratio [HR] 1.39, 95% confidence interval [CI] 0.53–3.7, p=0.51), but both groups had a higher risk of recurrence than the RES1 group (solitary metastasis). Indeed, the presence of a solitary metastasis was the only significant factor independently associated with recurrence. There was also no significant difference in the rate of hepatic recurrences between the COMB and RES2 groups (p=1.0). In the COMB group, there were two patients who recurred only in the liver; one of these was a recurrence at an ablation site and the other was at the resection margin.

The 5-year OS, measured from the time of initial reoperation was 52.3%, with no significant association with the use of ablation (p=0.19, Fig. 3). In univariate analysis, OS was associated with size of the largest metastasis (p=0.05) and the clinical risk score (p=0.0004), and a nonsignificant trend was noted with the

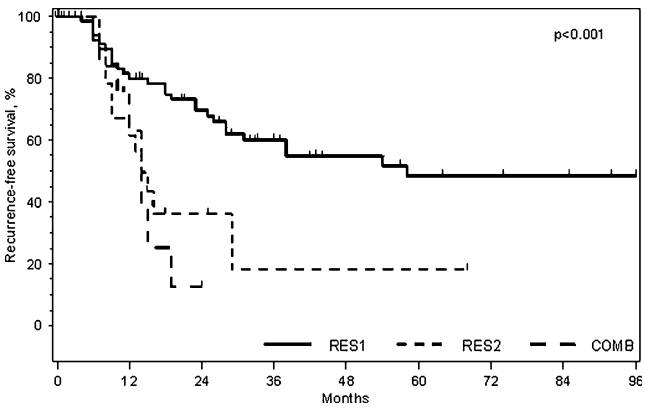

Fig. 2 Recurrence-free survival stratifed by multifocality and treatment. Overall, there was a difference in survival between the three groups, but there was no significant difference between resection and resection plus ablation in the setting of multiple metastases (RES2 vs. COMB)

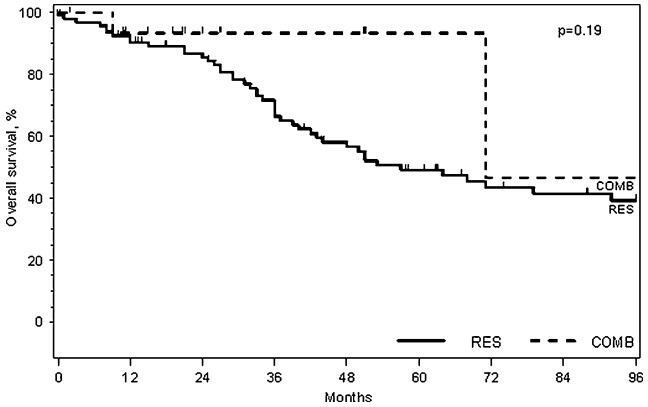

Fig. 3 Overall survival, stratified by treatment group

disease-free interval (p=0.11). In multivariable analysis, there was no significant difference between the COMB, RES1 (p=0.49), and RES2 (p=0.18) groups. There were no material differences when OS was measured from the time of each reoperation.

Discussion

After initial liver resection for colorectal liver metastases, the majority of patients recur, with many developing recurrent disease in the liver remnant.[2,16,27] Although curative reoperative liver resection can often be performed safely, it is technically difficult and can sometimes be unfeasible. In the present study, we evaluated the role of intraoperative ablation as an adjunct to surgical resection in the treatment of these patients. Over the study period, there was a marked increase in the use of intraoperative ablation from 0% in the early study period to 41% in the later study period. Intraoperative ablation was utilized in patients with multifocal rCLM and in those with higher baseline clinical risk scores, suggesting that these patients may have had more aggressive tumors. In addition to the increased use of ablation, there was a temporal increase in the incidence of abnormal liver parenchyma. Despite this, the ablation group had a significantly lower estimated blood loss and no increase in the risk of perioperative morbidity or mortality.

In this study, the group treated with combination resection and ablation was found to have a higher risk of liver recurrence than the resection-only group. In interpreting this finding, it is important to recognize that ablation combined with resection was only applied in the setting of multiple liver metastases, a factor that was strongly associated with recurrence. Indeed, when combination resection and ablation was assessed against a more comparable group—patients with multiple metastases treated with resection only—there was no significant difference in recurrence, with both groups having high recurrence rates and RFS of only 14 months. Nonetheless, the OS in this group remained modest with a 5-year OS of 49%. In addition, the use of intraoperative ablation did not compromise OS. It must be cautioned, however, that there was a relatively small number of patients treated with combination resection and ablation in this study.

Indeed, the factors most associated with recurrence and OS were not those related to treatment, but rather those related to tumor biology, such as the number of metastases and the size of the largest metastasis. Although we attempted to control for several tumor-related factors, it is important to acknowledge that the small number of patients in the COMB group limit the number of variables that can be controlled in multivariable analysis. In addition, the selection bias inherent to any retrospective study can lead to uncontrolled confounding variables that could impact the relationship between treatment and outcomes. A study by Gleisner et al.[28] confirmed, using propensity score methodology, that significant heterogeneity does exist when comparing patients treated with ablation with those treated with resection. Nevertheless, our findings do suggest a possible role for less radical and more parenchymal-sparing ablative approaches in selected patients with recurrent liver metastases, especially in those with multiple metastases as these patients have a high rate of recurrence, regardless of treatment. To date, many studies have reported on the safety and efficacy of surgical resection in the management of recurrent liver metastases.[4–15] However, few have examined the role that modern ablative technologies may play in this setting. Our findings are consistent with reports by van der Pool et al.[29] and de Jong et al.,[5] but are in contrast to the study by Abdalla et al.,[16] which suggested that both recurrence and OS were significantly worse in the group treated with ablation. This discordance may be explained by differences in patient populations wherein all patients in our study had recurrent liver metastases and thus were already selected to have more aggressive tumor biology. In addition, the relatively modest sample sizes in this and other studies suggest that issues related to patient selection may also account for dissimilarities between the studies.

Conclusions

In summary, our data suggest that in patients with rCLM, selective use of intraoperative ablation as an adjunct to resection may not compromise recurrence or OS. Oncologic outcomes in these patients may be more related to tumor biology than the specific treatment modality used. Indeed, ablation may be particularly useful in patients with multiple recurrent metastases and in whom complete resection is unfeasible. In these patients, ablation may be used to spare liver parenchyma with lower intraoperative blood loss,

similar rates of perioperative morbidity, and similar oncologic outcomes. However, additional studies with larger sample sizes may be warranted to further validate these findings.

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ORIGINAL ARTICLE

Significance of Platelet Count in the Outcomes of Hepatectomized Patients with Hepatocellular Carcinoma Exceeding the Milan Criteria

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Abstract
Background The appropriate treatment strategy for advanced hepatocellular carcinoma (HCC) that does not meet the Milan criteria (MC) is unclear. The aim of this study was to determine the significance of surgical treatment for such patients.
Study design From January 1990 to December 2007, 151 patients with HCC exceeding MC who underwent curative surgical treatment were enrolled. Survival and recurrence data and clinicopathological factors were examined. Prognostic factors were analyzed to identify those that contributed to improved surgical outcomes retrospectively.
Results After the initial hepatectomy, the overall 3-, 5-, and 10-year survival rates were 73%, 55%, and 33%, respectively, for the 151 patients in this study; the corresponding disease-free survival rates were 36%, 30%, and 17%, respectively. A platelet count under $10^5/mm^3$, multiple tumors, and liver cirrhosis of noncancerous tissue were adverse survival and disease-free survival factors by univariate analysis. Platelet count was an independent prognostic factor by multivariate analysis. The 3-, 5-, and 10-year overall survival rates of HCC exceeding MC in patients whose platelet count was $10^5/mm^3$ or greater reached 76%, 65%, and 44%, respectively, and were comparable with those that met MC (86%, 68%, and 37%, respectively).
Conclusions Hepatectomy for patients with advanced HCC exceeding MC improves survival, especially for patients with a sufficiently high platelet count, although recurrence rates after initial hepatectomy are high.

Keywords Hepatocellular carcinoma · Milan criteria · Platelet count · Advanced · Hepatectomy · Prognosis

Abbreviations

HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
OLT	Orthotopic liver transplantation
MC	Milan criteria
ICGR15	Indocianine green retention rate at 15 min
RFA	Radiofrequency ablation
LDLT	Living donor liver transplantation

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. There are various options to treat HCC, including partial hepatectomy, percutaneous ablation therapy, and transarterial chemoembolization (TACE). However, the resulting prognosis of HCC remains inadequate, despite technical refinements in these treatments, due to the high incidence of recurrence of HCC.[1,2]

Orthotopic liver transplantation (OLT) is the preferred treatment for patients with cirrhosis and early HCC per the

Milan criteria (MC: defined as a solitary HCC of a size <5 cm or 2 or 3 tumors <3 cm with no gross vascular invasion).[3] In patients with early HCC, such as within MC, as long as liver function is preserved, liver resection effects an overall 5-year survival rate that is comparable with that of liver transplantation, with minimal morbidity and mortality.[4–6]

The treatment strategy for advanced HCC exceeding MC has not been discussed sufficiently. Due to advanced tumor status, ablation therapy cannot be the first treatment, nor can OLT. Although hepatectomy or TACE is used to treat advanced HCC patients, the 5-year overall survival rate after curative hepatectomy for advanced HCC (tumor size, >5 cm) is 30% to 35%, and its recurrence after hepatectomy is unavoidable.[7,8]

We retrospectively analyzed the impact of hepatectomy on tumor control in patients with HCC exceeding MC. In this study, we examine the rationale for partial hepatectomy as an initial treatment and discuss the development of other strategies for recurrent HCC.

Methods

Patient data began to be collected prospectively by our program in 1986. Between January 1990 and December 2007, 781 consecutive adult patients underwent hepatectomy for HCC at Hiroshima University Hospital. A total of 651 consecutive HCC patients underwent curative intent hepatectomy in our hospital. Curative intent hepatectomy was defined as the removal of all recognizable tumors; patients with macroscopic vascular invasion in the first portal branch, portal vein trunk or hepatic vein trunk, and/or extrahepatic metastasis were excluded due to their poor prognosis.

Data for the remaining 622 HCC patients were included in the analysis. We divided the remaining patients into two groups: transplantable (meeting MC: single lesion with a maximum diameter <5 cm or three lesions with a maximum diameter <3 cm) and advanced (exceeding MC). We focused on the advanced group.

The indications and procedure for hepatectomy have been described.[9,10] Briefly, Child–Pugh class C was regarded as a contraindication for hepatectomy. The decision to perform hepatectomy was made based on liver function and extent of tumor. Liver function was assessed according to Child–Pugh classification and indocianine green retention rate at 15 min (ICGR15). In patients who lacked ascites and had normal bilirubin levels, ICGR15 became the chief determinant of resectability. For example, right hemihepatectomy could be tolerated if ICGR15 was in the normal range. One third of the liver parenchyma could be resected for patients with ICGR15 of 10–19%; segmentectomy was possible for patients with ICGR15 of 20–29%; and limited resection was possible for patients with ICGR15 of ≥30% (9.10).

Hepatectomy was indicated when all tumors could be resected with sufficient hepatic functional reserve, as determined by preoperative imaging. However, when the HCC tumors were hypovascular—suggesting that the tumor was well-differentiated HCC—and ≤2 cm and when the number of tumors ≤3, percutaneous ablation therapies were preferable despite hepatectomy being feasible, depending on the tumor location in the liver. Clinicopathological findings were recorded according to the criteria of the Liver Cancer Study Group in Japan.[11] Liver cirrhosis was confirmed by histological examination of the resected specimen.

A modified Clavien classification was used to grade the severity of postoperative complications.[12] Grade I complications were defined as deviations from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological intervention. Grade I complications also included wound infections that opened at the bedside.

Grade II complications were defined as those that required pharmacological treatment; blood transfusion and total parenteral nutrition were also included. Grade III complications were those that required surgical, endoscopic, or radiological intervention. Grade IV complications were life-threatening complications that required intermediate care/intensive care unit management. Grade V complications resulted in death. Operative mortality was defined as death within 30 days after surgery. In-hospital mortality was defined as death within the hospitalization period.

Postoperative follow-up evaluations consisted of a clinical physical examination, blood chemistry tests, and measurements of tumor marker levels, including alpha-fetoprotein and des-gamma-carboxy prothrombin, every month for 2 years. After 2 years, patients were assessed every 3 months. Patients were examined by abdominal ultrasonography every 3 months and by computed tomography every 6 months during the follow-up periods.

Our follow-up protocol included an evaluation by hepatologists to monitor cancer recurrence and the progress of chronic hepatitis or liver cirrhosis. When recurrence was noted in any of these examinations, patients underwent hepatic angiography. The patents were followed up regularly until December 31, 2008, and every patient was followed up for at least 6 months. All patients who experienced intrahepatic recurrence were managed with ablative therapy (radiofrequency ablation (RFA) or ethanol injection), TACE, or surgery, including liver transplantation, according to the same criteria as for the initial resection.

Statistical analyses were performed using unpaired Student's *t* test and chi-square test with Fisher's exact test. Overall survival and disease-free survival rates were calculated using the Kaplan–Meier method and compared using log-rank test. Disease-free survival was calculated, considering any death or recurrence as an event. A *P* value <0.05 was considered to be statistically significant. Statistical analysis was performed using StatView for Windows (Version 5.0; SAS Institute, Cary, NC, USA).

Results

As shown in Fig. 1, there were 151 patients with initially resectable advanced HCC who did not fulfill MC (i.e., exceeding MC) and 471 patients who met MC.

In the exceeding-MC group, the mean follow-up period for all survivors was 4.1±3.1 years (range, 0.5 to 14.5 years). Table 1 shows the patients' backgrounds. Overall operative mortality and in-hospital mortality rates were the same, i.e., 0.7% (n=1) in both conditions. The incidence of complications that developed after hepatectomy is also shown in Table 1. Thirty of the 151 patients (20%) had postoperative complications (Table 1). Nineteen of the 151 patients (13%) were grade III or more.

Figure 2a shows the survival rates of patients who underwent curative resection of HCC (meeting MC and exceeding MC). The survival rate of the exceeding-MC group was significantly lower than that of the group that met MC (P=0.030). The 3-, 5-, and 10-year survival rates

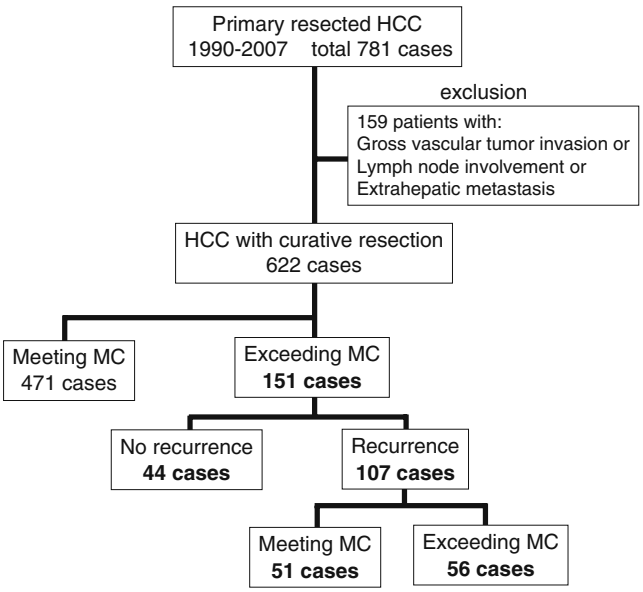

Fig. 1 Overview of outcomes of patients with primary resected hepatocellular carcinoma (HCC). The number of HCC patients who underwent curative resection was 622, subdivided by the Milan criteria (MC)

Table 1 Patients' backgroud

	Number of patients	Percent
Age (year)		
≤60	57	38.4
>60	94	61.6
Gender		
Male	127	84.1
Female	24	15.9
Type of hepatitis virus		
Non-HCV	61	40.4
HCV	90	59.6
Child–Pugh grade		
A	129	85.4
B	22	14.6
Type of hepatectomy		
Limited resection	82	54.3
Segmentectomy or more	69	45.7
Operative mortality: yes	1	0.7
In-hospital mortality: yes	1	0.7
Postoperative complications[a]: yes	30	19.9
Grade I, II	11	7.3
Grade III or more	19	12.6

[a] Postoperative complications was defined as any event satisfying the criteria advocated by Dindo et al.[12]

of the exceeding-MC group were 77%, 55%, and 33% and 86%, 68%, and 37% in those that met MC, respectively. The 3-, 5-, and 10-year disease-free survival rates of the exceeding-MC group were 36%, 30%, and 17% and 47%, 30%, and 13% in those that met MC, respectively (Fig. 2b).

Table 2 summarizes the results of the univariate analysis according to clinicopathological factors. A platelet count $<10^5/mm^3$ (P<0.001), multiple tumors (P=0.012), and cirrhosis of noncancerous tissue (P=0.035) were significant adverse prognostic factors for overall survival. Similarly, a platelet count $<10^5/mm^3$ (P=0.001), multiple tumors (P=0.005), and cirrhosis of noncancerous tissue (P=0.020) were significant adverse prognostic factors for disease-free survival.

By multivariate analysis, a platelet count $<10^5/mm^3$ (P=0.007) was found to be an independent adverse prognostic factor for overall survival (Table 3), and the 3-, 5-, and 10-year overall survival rates of patients with HCC exceeding MC whose platelet count was $\geq 10^5/mm^3$ were 76%, 65%, and 44%, respectively, comparable with the group that met MC (86%, 68%, and 37%, respectively; Fig. 2a). A platelet count $<10^5/mm^3$ (P=0.039) was also an independent adverse factor for disease-free survival (Table 3).

Out of 151, a total of 107 (71%) patients with HCC exceeding MC experienced a recurrence after the initial hepatectomy. Table 4 shows the patterns of cancer recurrence

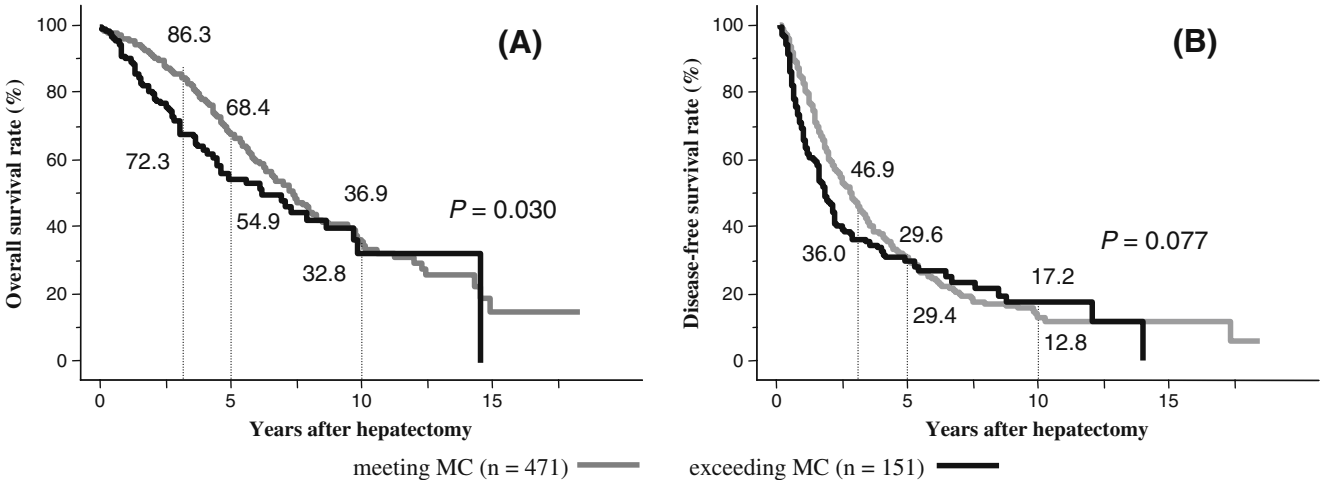

Fig. 2 Survival and disease-free survival curves of patients who received curative resection of HCC that met (471 patients) or were exceeding (151 patients) MC. (A) The 3-, 5-, and 10-y survival rates of patients exceeding MC were 72.3%, 54.9%, and 32.8%, respectively, and 86.3%, 68.4%, and 36.9%, respectively, in those who met MC. (B) The 3-, 5-, and 10-y disease-free survival rates of patients exceeding MC were 36.0%, 29.4%, and 17.2%, respectively, and 46.9%, 29.6%, and 12.8%, respectively, in those who met MC

and compares the consequent treatment details between patients whose platelet counts were $\geq 10^5/mm^3$ and $<10^5/mm^3$. The rate of HCC recurrence was significantly lower in patients whose platelet count was $\geq 10^5/mm^3$; 76 (66%) of such patients experienced a recurrence of HCC after hepatectomy, as compared to 31 (89%) patients whose platelet count was $<10^5/mm^3$ (P=0.009). Further, regarding the pattern of recurrence, the proportion of patients who had a recurrence of HCC that met MC was significantly higher in patients with a platelet count$\geq 10^5/mm^3$ than those with a platelet count of $<10^5/mm^3$ (51% vs. 39%; P<0.001).

The proportion of patients who received curative treatment for the first recurrence, such as repeat hepatectomy and local ablation therapy, had significantly higher platelet counts, i.e., $\geq 10^5/mm^3$ (44% vs. 23%; P=0.047).

Of the 107 patients who experienced a recurrence, 51 (48%) met MC and 56 (52%) were exceeding MC, including extrahepatic recurrence (Fig. 1). The 3- and 5-year survival rates after recurrence were significantly superior in patients with a recurrence that met MC (71% and 40%, respectively) than those exceeding MC (17% and 9%) (P<0.001; Fig. 3).

Table 5 shows the details of the treatments for recurrences after hepatectomy. The proportions of patients who received ablation therapy or repeat hepatectomy after recurrence was higher in patients with a recurrence that met MC than those exceeding MC (P=0.001). Two patients with a recurrence that met MC, who underwent salvage living donor liver transplantation (LDLT), did not have a recurrence after liver transplantation at the 2- and 3-year follow-up, respectively. One patient with a recurrence that was exceeding MC, and who underwent salvage LDLT, experienced a recurrence of HCC within 1.5 years.

Discussion

The ultimate goal of a treatment for HCC is to prolong survival by eradicating malignant legions while preserving hepatic function. Surgical resection, by partial hepatectomy or total hepatectomy followed by OLT, is the standard treatment with a curative intent.[13] The resectability and choice of procedure depend on many factors, including baseline liver function, absence of extrahepatic metastasis, size of residual liver, availability of resources (including liver grafts), and expertise of the surgical team.

Although hepatic resection, ablation therapy, and liver transplantation are accepted, effective treatments for patients with cirrhosis and early HCC, the proper strategy for advanced HCC has not been established. Therefore, we studied HCC patients who were exceeding MC—who are not eligible for OLT as the initial treatment. We investigated the impact of hepatectomy on outcomes of HCC that exceeded MC and examined the rationale of hepatectomy as an initial treatment for HCC exceeding MC.

In our series, the 5- and 10-year survival rates of patients with HCC exceeding MC were 55% and 33%, respectively, comparable with Kamiyama et al.[14] We also identified significant prognostic factors of patients with HCC exceeding MC who underwent hepatectomy: platelet count, tumor number, and cirrhosis. Moreover, our multivariate analysis revealed that platelet count was the sole independent prognostic factor in these HCC patients.

The prognosis of such patients after hepatectomy was clearly stratified by platelet count, which is typically predictable by preoperative laboratory tests. The 3-, 5-, and 10-year overall survival rates of patients with HCC exceeding MC, whose platelet count was $\geq 10^5/mm^3$, were

Table 2 Overall and disease-free survival rates of patients with HCC exceeding MC according to clinicopathological factor

		Overall survival (%)				Disease-free survival (%)			
		3-year	5-year	10-year	*P* value	3-year	5-year	10-year	*P* value
All cases (n=151)		73	55	33		36	30	17	
Age (year)	≤60 (n=57)	69	58	38	0.873	35	28	17	0.977
	>60 (n=94)	74	53	30		37	30	18	
Gender	Male (n=127)	75	55	34	0.647	34	27	15	0.247
	Female (n=24)	61	56			45	45		
Type of hepatitis virus	Non-HCV (n=61)	71	65	36	0.498	46	39	25	0.054
	HCV (n=90)	73	50	32		29	22	12	
Total bilirubin (/mm^3)	<1.0 (n=125)	71	52	32	0.151	37	32	19	0.515
	≥1.0 (n=26)	78	72	36		30	19	9	
Platelet counts (/mm^3)	<10^5 (n=35)	61	27		< 0.001	16	8		0.001
	≥10^5 (n=116)	76	65	44		42	36	21	
ALT (IU/I)	<60 (n=106)	71	49	29	0.08	36	30	15	0.707
	≥60 (n=45)	77	70	45		36	27	18	
Alb (g/dL)	<3.5 (n=37)	73	52	41	0.995	42	31	23	0.55
	≥3.5 (n=114)	73	58	32		35	29	15	
ICG-R15 (%)	<20 (n=111)	72	57	43	0.303	40	32	20	0.467
	≥20 (n=39)	75	52			26	22		
Child–Pugh grade	A (n=129)	73	56	30	0.643	35	29	18	0.645
	B (n=22)	72	54	46		43	32	17	
AFP (ng/mL)	<400 (n=101)	77	56	31	0.905	33	26	16	0.495
	≥400 (n=48)	65	55	41		45	39	22	
Number of tumors	Single (n=60)	79	71	52	0.012	52	41	28	0.005
	Mutiple (n=91)	68	45	23		26	22	12	
Tumor distribution	One section (n=77)	81	56	43	0.083	42	33	28	0.091
	more (n=74)	61	55	25		32	23	8	
Non-cancer tissue	Cirrhosis (n=52)	67	39	29	0.035	23	15	8	0.02
	Others (n=99)	75	65	38		42	36	23	
Preoperative TAE	Yes (n=102)	72	55	30	0.91	35	28	15	0.366
	No (n=45)	73	56	50		40	33	25	
Type of hepatectomy	Limited resection (n=82)	73	51	29	0.743	34	27	8	0.472
	Segmentectomy or more (n=69)	71	60	39		39	33	33	
Transfusion	Yes (n=20)	64	46	0	0.071	25	17	0	0.103
	No (n=131)	74	57	37		38	31	21	
Microscopic vascular invasion	Yes (n=74)	60	48	30	0.089	30	28	17	0.144
	No (n=77)	84	61	35		42	31	18	
Histologic grading	Well or moderate (n=122)	71	55	30	0.718	34	28	18	0.777
	poor (n=26)	74	52	43		42	31	12	
Diabetes mellitus	Yes (n=53)	73	58	34	0.929	39	30	17	0.493
	No (n=95)	72	52	31		33	29	17	
SF criteria	Meeting SF (n=59)	74	52	23	0.704	30	28	15	0.734
	Exceeding SF (n=92)	71	57	38		40	32	19	

HCC hepatocellular carcinoma, *MC* Milan criteria, *ALT* alanine aminotransferase, *ICG-R15* indocianine green retension rate at 15 min, *AFP* alpha-fetoprotein, *SF* San Francisco criteria (1 lesion <6.5 cm, 2–3 lesions each <4.5 cm with total diameter <8 cm)

76%, 65%, and 44%, respectively, comparable with those that met MC (86%, 68%, and 37%, respectively).

Hepatectomy should be the first-line treatment in patients with HCC exceeding MC whose platelet count is >10^5/mm^3.

Table 3 Results of Cox's proportional hazards analysis for overall and disease-free survival after hepatectomy

Variables	*P* value	Relative risk	95% CI
Overall survival			
Plt. Count: $<10^5/mm^3$	0.007	2.155	1.232–3.774
Number of tumors: multiple	0.103	1.65	0.903–3.021
Tumor distribution: more than one section	0.168	1.439	0.858–2.410
Transfusion: Yes	0.13	1.667	0.861–3.228
Microscopic vascular invasion: Yes	0.067	1.596	0.969–2.629
Non-cancer tissue: cirrohsis	0.488	1.207	0.709–2.058
Disease-free survival			
HCV infection: Yes	0.585	1.148	0.699–1.887
Plt. Count: $<10^5/mm^3$	0.039	1.653	1.025–2.667
Number of tumors: multiple	0.202	1.368	0.845–2.221
Tumor distribution: more than one section	0.098	1.412	0.939–2.123
Non cancer tissue: cirrohsis	0.274	1.277	0.824–1.979

In general, platelet count, which reflects the severity of portal hypertension, is a significant predictor of survival. Several studies have shown that platelet count is a risk factor for carcinogenesis from chronic hepatitis and for survival and recurrence of HCC after treatment, including liver resection.[15–18] In fact, we observed that recurrence of HCC after hepatectomy decreased in patients whose platelet count was $\geq 10^5/mm^3$ and that the proportion of patients who experienced a recurrence of HCC that met MC was significantly higher in patients with a platelet count $<10^5/mm^3$. Further, the proportion of patients who underwent repeat hepatectomy or RFA as a curative treatment for a recurrence of HCC was significantly higher in patients whose platelet count was $\geq 10^5/mm^3$.

After resection with curative intent, many patients experience a recurrence, which is a significant cause of late death. In this study, the recurrence rate was high: 70.9% of patients with HCC exceeding MC were diagnosed as having had a recurrence (mean follow-up, 4.1 years). Tumor number was an independent factor of disease-free survival, and the 3-, 5-, and 10-year disease-free survival rates were 51%, 41%, and 28%, respectively, even in patients with a single tumor.

The reported cumulative 5-year recurrence rates range from 50% to 100%.[19–22] In our series, 107 (71%) of 151 patients with HCC exceeding MC experienced a recurrence of HCC, 51 (48%) of whom met MC. These results demonstrate that downstaging a recurrence to within MC was achieved by hepatectomy as an initial treatment for HCC exceeding MC. The proportion of patients who underwent repeat hepatectomy or local ablation therapy as a curative treatment for HCC recurrence was significantly higher in patients with a recurrence of HCC within MC versus exceeding MC. The outcomes after recurrence were significantly better in patients whose recurrence was downstaged to within MC compared with those who did

Table 4 Recurrent pattern and treatment of recurrent HCC after hepatectomy (comparison with platelet counts)

	Platelet counts $>10^5$ (n=116)	Platelet counts $<10^5$ (n=35)	*P* value
Cancer recurrence[a]: yes	76 (66)	31 (89)	0.009[c]
Recurrent pattern[b]			<0.001[c]
Meeting MC	39 (51)	12 (39)	
Exceeding MC or extrahepatic recurrence	37 (49)	19 (61)	
Treatments for recurrence[b]			0.047[c]
Curative treatment	34 (44)	7 (23)	
Non-curative treatment	41 (55)	22 (70)	
Salvage liver transplantation	1 (1)	2 (6)	

Curative treatment included partial hepatectomy, local ablation therapy; non-curative treatment included transarterial chemoembolization, systemic chemotherapy, radiation therapy and conservative

HCC hepatocellular carcinoma, *MC* Milan criteria

[a] Data are expressed as the number of patients (percentage of total patients)

[b] Data are expressed as the number of patients (percentage of patients who had a recurrence)

[c] Statistically significant difference

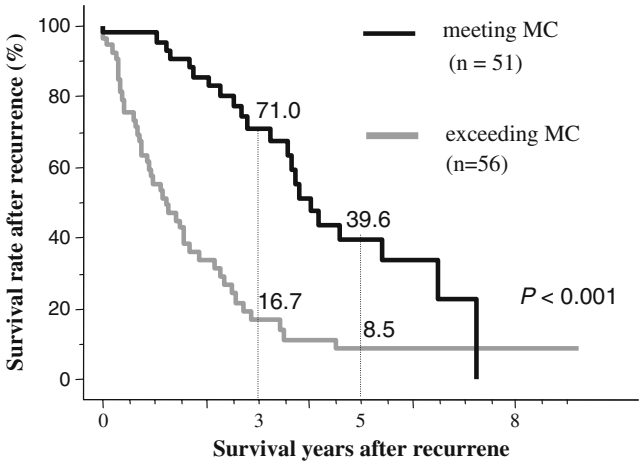

Fig. 3 Comparison of survival curves after recurrence of HCC according to recurrent pattern. The 3-and 5-year survival rates of patients with a recurrence that met MC were 71.0% and 39.6%, respectively, and 16.7% and 8.5%, respectively, in those who exceeding MC including extrahepatic recurrence

not achieve such downstaging. These results indicate that hepatectomy as an initial treatment is an important component of the treatment strategy for HCC exceeding MC.[23]

With regard to the treatment of recurrent HCC patients, we reported that the more hepatectomy was repeated, the shorter the recurrence-free interval became, suggesting a limitation of repeat hepatectomy in curing recurrent HCC.[24] Liver transplantation has been discussed as the next strategy to treat tumor recurrences after initial hepatectomy in patients with advanced HCC. Several studies have reported salvage transplantation for recurrence after hepatectomy,[6,25–27] suggesting that primary hepatectomy and salvage liver transplantation is a feasible and rational strategy for patients with small HCC that preserves liver function. In this series, of the patients who had recurrence after resection for tumors exceeding MC, approximately 48% had recurrent tumors that were within MC. This result also indicates that approximately half of the patients with recurrence would be candidates for salvage liver transplantation after partial hepatectomy performed for downstaging to within MC. Salvage LDLTs were adopted for three patients, two of whom, who had a recurrence that met MC, did not experience a recurrence after salvage LDLT at the 2- and 3-year follow-up, respectively. Yao et al. and Ravaioli et al. reported that locoregional treatments, including RFA, were effective for downstaging prior to liver transplantation.[23,28] In general, RFA was indicated for HCCs with diameters less than 3 cm. Although RFA may be effective for downstaging multiple small HCCs, its effectiveness may be limited in the case of downstaging large HCCs with diameters greater than 3 cm. Further studies are required to clarify the indications for the use of RFA and hepatectomy as downstaging modalities prior to liver transplantation.

A significant proportion of patients with HCC exceeding MC might benefit from liver transplantation. Mazzaferro et al. proposed an expansion of the indications for liver transplantation, using up to seven criteria.[29] Takada et al. demonstrated that LDLT could be safely extended to ≤10 tumors (all ≤5 cm in diameter and PIVA-II ≤ 400 mAU/mL) with acceptable outcomes.[30] Liver transplantation has been proposed as an initial treatment for patients with HCC exceeding MC whose platelet count is $<10^5/mm^3$, although the extension of the indications of liver transplantation is restricted.

Conclusion

Hepatectomy for patients with HCC exceeding MC increases survival rates, especially for patients with sufficiently high platelet counts, although their recurrence rates

Table 5 Treatments for recurrent HCC after initial hepatectomy

Modalities	Recurrent pattern *N* (%)[a]		*P* value
	Meeting MC (*n*=51)	Exceeding MC or extrahepatic (*n*=56)	
Partial hepatectomy	10 (20)	5 (9)	<0.001[b]
Salvage liver transplantation	2 (4)	1 (2)	
Resection of distant metastasis	0	3 (5)	
Percutaneous ablation therapy	18 (35)	8 (14)	
TACE	21 (41)	23 (41)	
Chemotheraphy and/or radiation	0	10 (18)	
Non-treatment	0	6 (11)	

MC Milan criteria, *TACE* transarterial chemoembolization

[a] Data are expressed as the number of patients (percentage of patients who had a recurrence of each group)

[b] Statistically significant difference

after initial hepatectomy are high. Hepatectomy as an initial treatment is an important component of the treatment for HCC exceeding MC to downstage the recurrence to within MC.

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ORIGINAL ARTICLE

Appropriate Treatment Strategy for Intrahepatic Recurrence After Curative Hepatectomy for Hepatocellular Carcinoma

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Abstract
Introduction The aim of this study is to evaluate the appropriate treatment for intrahepatic recurrence after hepatectomy for hepatocellular carcinoma (HCC).
Methods Of 151 patients who underwent initial hepatectomy for HCC, 82 had intrahepatic recurrence and were divided into two groups: group A, ≤2 tumors, each 3 cm in size; and group B, beyond the group A. Survival and treatment in each group were analyzed retrospectively to determine the best therapeutic modality for intrahepatic recurrence.
Results The 5-year overall survival and recurrence rate were 65% and 58%, respectively. Overall 1-, 3-, and 5-year survival rates after recurrence were better in group A (100%, 76%, and 54%) than in group B (74%, 23%, and 5.8%; $p<0.001$). The clinical backgrounds were not different for each modality. Of the 43 patients in group A, 10 underwent hepatectomy, 21 ablation therapy, and 12 transcatheter arterial chemoembolization (TACE). The survival rate of hepatectomy was similar to that of ablation therapy and significantly better than that of TACE ($p=0.0248$). Of the 39 patients in group B, the results of TACE were similar to other therapies after recurrence.
Conclusions Repeat hepatectomy and ablation therapy were more effective than TACE in the group with ≤2 tumors up to 3 cm in size at recurrence, while any treatment modality was more effective than best supportive care, but the outcome was poorer in the group with ≥3 tumors or tumor size ≥3 cm at recurrence.

Keywords Hepatocellular carcinoma (HCC) · Intrahepatic recurrence · Recurrent treatment

Introduction

Recently, the surgical techniques for liver resection have improved, and hepatectomy has been established as a curative treatment for hepatocellular carcinoma (HCC).[1,2] However, the long-term prognosis after curative resection is unsatisfactory, because of the high incidence of recurrence. Several studies have reported that the cumulative 5-year recurrence rate was 70% to 80%, and the most common site of recurrence was remnant liver.[3–5] Appropriate treatment for intrahepatic recurrence is important for improving long-term outcome after resection, and current modalities include hepatectomy, local ablation therapy, and transcatheter arterial chemoembolization (TACE). It has been suggested that repeat resection is the most effective treatment, with a 5-year survival rate from 37% to 70% in selected patients.[4–7] In addition, several studies have recently reported that ablation therapies, percutaneous ethanol injection (PEIT) and radiofrequency ablation (RFA), were also effective after hepatectomy.[8–10] However, TACE has been performed in most cases of intrahepatic recurrence with multiple tumors, unfavorable tumor location, and poor liver function, with a relatively poor 5-year survival rate from 0% to 27%, even with repeated TACE.[11,12] On the other hand, liver transplantation might be the ideal treatment for both recurrent tumors and deteriorated liver function in

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patients with intrahepatic recurrence.[13,14] The severe disparity between the demand for transplantation and the supply of organs from deceased donors has precluded an expansion of the selection criteria to patients with HCC.[15]

In this study, the most effective treatment modalities for intrahepatic recurrent HCC were retrospectively evaluated by number and size of recurrent tumors (e.g., up to two tumors and each ≤3 cm in size).

Material and Methods

From October 1998 to October 2008, 199 initial hepatectomies for HCC were performed at Osaka Medical College Hospital. Forty-eight patients were excluded for the following reasons: seven died in hospital after hepatectomy, 12 died of other disease-related causes during follow-up, 15 underwent noncurative resection, and 14 were lost to follow-up after discharge.

There were 112 men and 39 women, with a mean age of 68.5 years (range, 33–83 years). Of these, 28 (18.5%) were positive for serum hepatitis B surface antigen (HBsAg), 81 (53.6%) were positive for serum antihepatitis C virus antibodies, and two (3.3%) were positive for both. Liver cirrhosis was present in 55 patients (36.4%) and 18 patients (11.9%) were Child-Pugh class B.

Anatomical resections (defined as segmentectomy or hemi-hepatectomy) were performed in 61 patients (40.4%).

Tumor size, number, histology (well or moderately differentiated vs. poorly differentiated), macroscopic classification (simple nodular type vs. simple nodular type with extranodular growth and/or confluent multinodular type), vascular invasion (microscopic portal and/or hepatic vein invasion), surgical margin status, and background liver histology were diagnosed by two pathologists.

After discharge, the patients were followed-up at 2 months after surgery and then every 1–2 months. All patients were screened for the tumor marker, alpha-fetoprotein, and protein induced by vitamin K absence or antagonist II (PIVKA II) every 1–2 months, and underwent abdominal ultrasonography or enhanced computed tomography (CT) every 3–4 months. Suspected intrahepatic recurrence was confirmed by enhanced magnetic resonance imaging and CT. Extrahepatic recurrence was also confirmed using a chest CT and a bone scintigram. Intra- and/or extrahepatic recurrence developed in 90 of the 151 patients. The 82 patients with only intrahepatic recurrence were the focus of this study. The patients were divided into two groups on the basis of recurrence patterns: group A, with up to two recurrent tumors, each equal to or smaller than 3 cm; and group B, with recurrent tumors beyond the criteria for group A.

Treatment Strategy

If tumors recurred, we assessed for underlying liver function, and the size and location of the tumor before treatment. The selection criteria for repeat hepatectomy were essentially the same as those for initial hepatectomy: i.e., the presence or absence of ascites, the serum total bilirubin level, and the indocyanine green retention rate at 15 min (ICG R15).[16] Basically, local ablation therapy (PEIT or RFA) was chosen for small tumors size (up to 3 cm) and numbers (two or less). TACE could be given to any patient not presenting with tumor thrombus in the major portal branches. All patients were informed of the possible benefits and complications of each treatment, and either repeat hepatectomy or ablation therapy was recommended. Patients who refused repeat hepatectomy or those with tumors in sites too difficult for ablation therapy underwent TACE treatment.

Statistical Analysis

Continuous variables are expressed as medians or mean± standard deviation. Continuous variables were compared using Student's t test. Statistical comparisons between the two groups were made using the χ^2 test, Fisher's exact test, and the Mann–Whitney U test for nonparametric data. Factors that were found to be significant on univariate analysis were also subjected to multivariate logistic regression analysis to determine adjusted odds ratios. Overall survival rates were calculated by the Kaplan–Meier method using the log-rank test to analyze differences. All analyses were performed using the JMP version 7.0.2 software package (SAS Institute, Cary, NC, USA) under Mac OS X. Values of $p<0.05$ were considered significant.

Results

Intrahepatic recurrence was seen in a total of 82 patients and these patients were divided into two groups: group A, 43 patients with up to two tumors, each ≤3 cm in size, and group B, 39 patients with three tumors or tumors >3 cm in size.

The overall and disease-free survival rates after initial hepatectomy for the 151 patients are shown in Fig. 1; the 1-, 3-, and 5-year overall survival rates were 94%, 81%, and 65%, respectively. The 5-year cumulative recurrence rate was 58%.

The overall survival rates after recurrence according to the recurrence patterns are shown in Fig. 2. Overall 1-, 3-, and 5-year survival rates after recurrence were better in group A (100%, 76%, and 54%, respectively) than in group B (74%, 23%, and 5.8%, respectively; $p<0.001$).

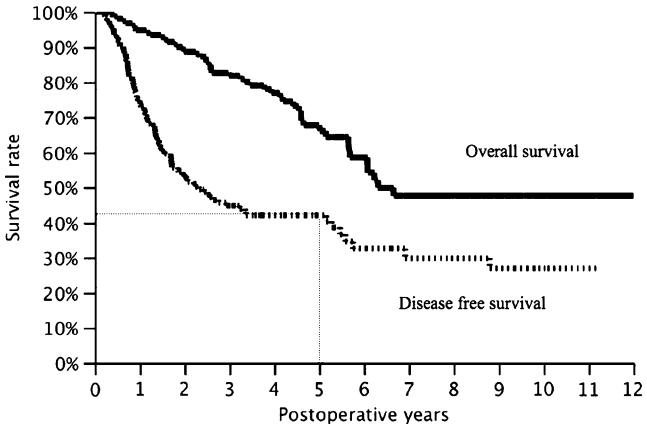

Fig. 1 Overall and disease-free survival rates after initial hepatectomy for the 151 patients. The 1-, 3-, and 5-year overall survival rates were 94%, 81%, and 65%, respectively. The 5-year cumulative recurrence rate was 58%

The clinical backgrounds at initial hepatectomy and at recurrence for each therapeutic modality in group A are shown in Table 1. The location of the tumor was distributed uniformly in the remnant liver. Pathological liver cirrhosis was seen in three patients who underwent repeat hepatectomy (30%), eight patients who underwent ablation therapy (38%), and four patients who underwent TACE therapy (33%). Liver function at recurrence was well preserved in all three groups, without any significant differences among them. Two patients who underwent repeat hepatectomy (20%), three patients who underwent ablation therapy (14%), and four patients who underwent TACE therapy (33%) were Child-Pugh B. Multiple tumors at the time of recurrence were seen in three patients who underwent repeat hepatectomy (30%), five patients who underwent ablation therapy (24%), and seven patients who underwent TACE therapy (58%). The median recurrence-free interval after initial hepatectomy was 22.8 months with repeat hepatectomy, 17.6 months with ablation therapy, and 18.5 months with TACE therapy.

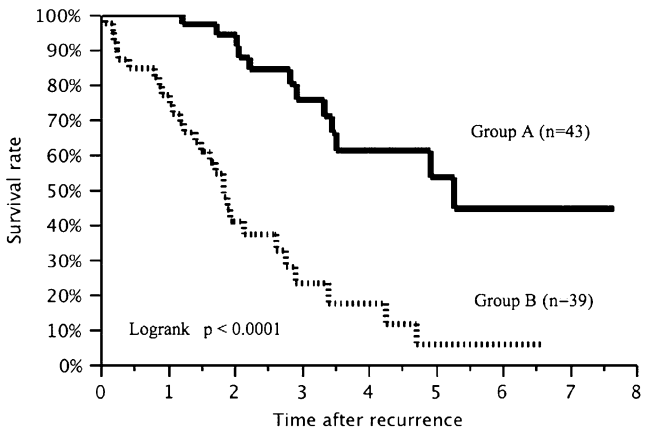

Fig. 2 Overall survival rates after recurrence according to the recurrent patterns. *Group A* ≤2 tumors, each equal to or smaller than 3 cm, *group B* recurrent tumors beyond the criteria for group A. Overall 1-, 3-, and 5-year survival rates after recurrence were better in group A (100%, 76%, and 54%, respectively) than in group B (74%, 23%, and 5.8%, respectively; $p<0.001$)

The overall survival rate after recurrence for each therapeutic modality in group A is shown in Fig. 3. Of the 43 patients in group A, 10 underwent repeat hepatectomy, 21 received ablation therapy, and 12 underwent TACE. Overall, 15 of 24 patients in the ablation group received RFA during the early period, and five received PEIT. The survival rate of repeat hepatectomy group was statistically similar to those of ablation therapy after recurrence, though repeat hepatectomy appeared superior to that in the ablation group beyond 5 years. TACE therapy was significantly worse than either therapy ($p=0.0248$ vs. hepatectomy), presumably due to insufficiency in controlling recurrent HCC compared with the other modalities.

The recurrence-free survival rate after initial hepatectomy in patients with up to two tumors, each ≤3 cm in size and each treatment received in group A is shown in Fig. 4. The recurrence-free survival rate for repeat hepatectomy was similar to that after initial hepatectomy. TACE therapy was significantly worse than repeat hepatectomy ($p=0.0449$).

The overall survival rate after recurrence for each therapeutic modality in group B is shown in Fig. 5. Of the 39 patients in group B, 26 underwent TACE, eight received modalities other than TACE (repeat hepatectomy, three; PEIT, five), and five received no therapy. All patients died within 1 year in the non-therapy group. The results of TACE were similar to other treatments after recurrence.

Discussion

Hepatic resection has been established as a curative treatment for HCC worldwide. However, the long-term prognosis after curative resection remains unsatisfactory because of the high rate of recurrence. Cumulative 5-year recurrence rates after curative resection are 70% to 80% and 80% to 95% of such recurrences are confined to the remnant liver.[4,5,17–19] The 5-year cumulative recurrence rate after initial hepatectomy was 58% in this study, and treatment of recurrence is extremely important. Therefore, appropriate management of recurrent HCC is central to improving the long-term outcome after initial hepatectomy. Although various therapeutic modalities, such as repeat hepatectomy, ablation, and TACE, have been used to treat recurrent HCC, there are no standard strategies for selecting the modality. When treatment of recurrence was considered, liver function was of significant importance, as well as initial treatment. If the liver function was poor, only TACE

Table 1 Clinical backgrounds at initial hepatectomy and at recurrence for the three treatment modalities in group A

Factors	Hepatectomy (n=10)	Ablation (n=21)	TACE (n=12)	P values
Patients condition at first hepatectomy				
Age (years)[a]	69 (50–79)	67 (50–79)	70 (58–80)	NS
Gender (male/female)[b]	8/2	17/4	7/5	NS
Virus infection[b]	5 (50%)	13 (62%)	10 (83%)	NS
Anti-virus therapy[b]	3 (30%)	5 (24%)	4 (33%)	NS
Diabetes mellitus[b]	3 (30%)	4 (19%)	4 (33%)	NS
Child-Pugh B[b]	1 (10%)	3 (14%)	3 (25%)	NS
Tumor number: multiple[b]	3 (30%)	5 (24%)	6 (50%)	NS
Vascular invasion[b]	2 (20%)	1 (5%)	1 (8%)	NS
Tumor diameter (cm)[c]	4.6±4.1	2.8±1.6	4.0±1.6	NS
Intrahepatic metastasis[b]	2 (20%)	1 (5%)	1 (8%)	NS
Liver cirrhosis[b]	3 (30%)	8 (38%)	4 (33%)	NS
Condition at recurrence				
Child-Pugh B[b]	2 (20%)	3 (14%)	4 (33%)	NS
Tumor number: multiple[b]	3 (30%)	5 (24%)	7 (58%)	NS
Tumor diameter (cm)[c]	1.9±0.7	1.7±0.6	1.5±0.5	NS
Recurrence location[b]				
Segment 1	1	0	0	
Segment 2/3/4	6	9	6	
Segment 5/8	5	11	8	
Segment 6/7	1	6	5	
Recurrence-free interval after initial hepatectomy (month)[a]	22.8 (8.8–120)	7.6 (2.9–64.2)	18.5 (8.0–33.5)	NS

TACE transcatheter arterial chemoembolization, *vascular invasion* microscopic portal and/or hepatic vein invasion, *NS* not significant

[a] Data are median (range)

[b] Data are no of patients

[c] Data are the mean±SD

was selected, without considering other treatment. Thus, given the selection bias, an accurate assessment of the therapeutic modalities cannot be made. In this retrospective study, we settled the criteria "≤2 tumors each 3 cm in size at

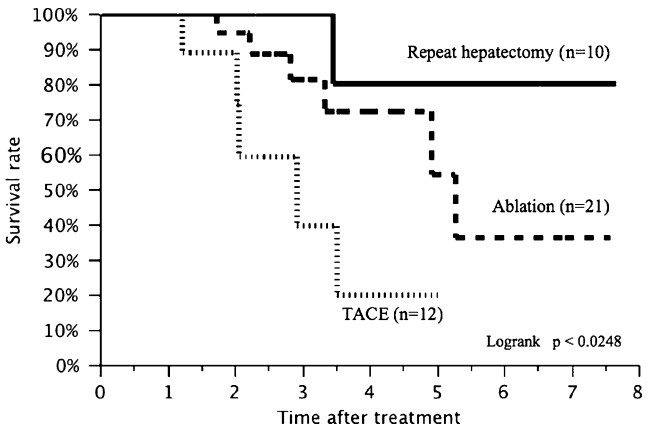

Fig. 3 Overall survival rate after recurrence for each therapeutic modality in group A (n=43). The survival rates of repeat hepatectomy were similar to those of ablation therapy after recurrence. Transcatheter arterial chemoembolization therapy was significantly worse than either therapy (p=0.0248 vs. hepatectomy)

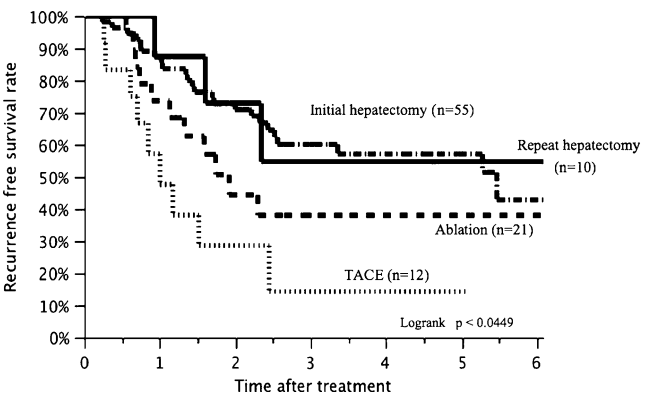

Fig. 4 Recurrence-free survival rate after initial hepatectomy in patients with up to two tumors, each ≤3 cm in size and each treatment received in group A. The recurrence-free survival rate for repeat hepatectomy was similar to that after initial hepatectomy. Transcatheter arterial chemoembolization therapy was significantly worse than repeat hepatectomy (p=0.0449)

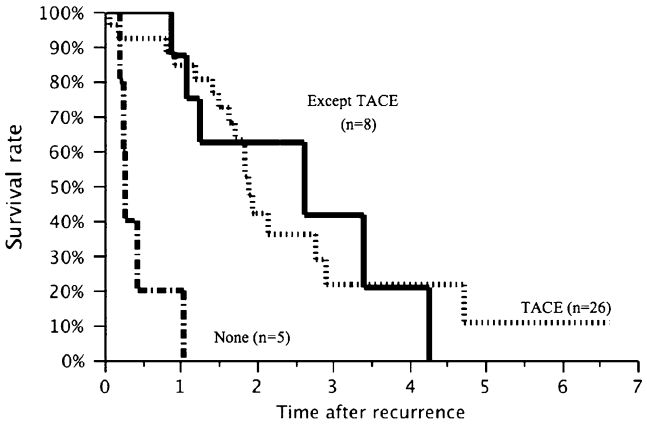

Fig. 5 Overall survival rate after recurrence for each therapeutic modality in group B (n=39). All patients died within 1 year in the non-therapy group. The results of transcatheter arterial chemoembolization therapy were similar to other treatments after recurrence

recurrence", which was also the selection criteria for local ablation therapy including PEIT or RFA, in an attempt to minimize selection bias as possible. We have confirmed that no significant difference in the patient background between the treatment modalities was observed when using this criterion. More importantly, under this condition, these three modalities were evenly expected to achieve their efficacy with a curative intent.

The safety of repeat hepatectomy has already been established, with operative mortality rates from 0% to 8.5%, and repeat hepatectomy was performed as the most effective therapy, with the 5-year survival rate after repeat hepatectomy ranging from 37% to 70%. Actually, the rate of repeat hepatectomy for recurrent HCC has been recently reported to be 10% to 31%,[6,20–27] and the rate was 11% in this study. Minagawa,[7] Shimada,[23], and Hu et al.[26] reported that a recurrence-free interval of less than 1 year after initial hepatectomy, four or more tumors, Edmondson and Steiner's grade 3 at repeat hepatectomy, and portal invasion at initial or repeat hepatectomy were significant predictors of a poor prognosis. In this study, the 5-year survival rate after repeat hepatectomy was 80%, which was a good outcome, as in other reports. Moreover, in group A, the recurrence-free survival rate after repeat hepatectomy in group A was similar to that after initial hepatectomy, which suggests that repeat hepatectomy may be appropriate in group A.

Meanwhile, the efficacy of ablation therapy, including RFA, for initial treatment of HCC has recently been reported and become well known. In recurrent HCC, Liag et al. reported that for ≤3 tumors up to 5 cm in size, the efficacy of minimally invasive RFA was similar to that of repeat hepatectomy, with 5-year survival rates after repeat treatment of 27.6% vs. 39.9%.[28] However, drawbacks of RFA, including insufficient treatment of tumors near the surface or vessels, and the risk of causing dissemination, have been pointed out.[29,30] In our results as well, in the group with ≤2 tumors up to 3 cm in size at recurrence, no statistically significant differences were seen between hepatectomy and ablation in recurrence-free survival or overall survival rates, though the survival rate in the hepatectomy group appeared substantially superior to that in the ablation group beyond 5 years. More accumulation of clinical data is required to conclude regarding long-term outcomes of these two modalities, repeat hepatectomy vs. ablation therapy, beyond 5 years post-treatment for recurrence.

TACE therapy is now widely performed for intrahepatic recurrences. However, in terms of local control, compared to repeat resection or ablation, inferior results may be inevitable. The prognosis with TACE therapy after repeat hepatectomy is very poor, with reported 5-year survival rates of 0–27%.[6,11,12] In our results as well, in the group with ≤2 tumors up to 3 cm in size at recurrence, TACE therapy was significantly worse than hepatectomy. In the groups with ≥3 tumors or tumors >3 cm in size at recurrence, however, TACE provided results similar to surgery or ablation. In patients with poor liver function or unfavorable tumor conditions, TACE may become an effective treatment method, and perhaps the treatment of first choice.

Finally, remnant recurrences include intrahepatic metastases and multicentric occurrence. Intrahepatic metastases, despite being thought to be hematogenous metastases, remain localized in the liver for a long time after diagnosis and do not metastasize to other organs. Therefore, it has also been reported that most may actually be multicentric HCC.[31] In particular, with a background of viral infection, even with hepatectomy, cancer occurs at constant rates. Therefore, liver transplantation in which the underlying damaged liver and tumor can be replaced at the same time, may be the ideal treatment. Belghiti et al. recommend hepatic resection as the first choice, then in cases of recurrence or decreased liver function during follow-up, they recommend "salvage transplantation".[32] However, because of various problems, including donor issues, this is difficult to accept as standard therapy at the present time. Finally, the usefulness of anticancer drug as adjuvant treatment in prevention of recurrence remains controversial, but with the advent of Sorafenib, attention is focused on future expansion of such treatment.

Conclusion

If we consider the high recurrence rates after hepatectomy for HCC, then besides initial treatment, treatment for recurrence after hepatectomy must also be thoroughly investigated. In the group with ≤2 tumors up to 3 cm in size at recurrence, the prognosis was better with repeat hepatectomy and ablation therapy than with TACE therapy.

However, in the group with ≥3 tumors or tumor size ≥3 cm at recurrence, any treatment modality including TACE was more effective than best supportive care alone, but the overall outcome was poorer.

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ORIGINAL ARTICLE

Overexpression of Matrix Metalloproteinase-21 is Associated with Poor Overall Survival of Patients with Colorectal Cancer

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Abstract
Introduction Matrix metalloproteinase-21 (MMP-21) is a member of the MMP family, which is overexpressed in some solid tumors and is thought to enhance the tumor invasion and metastasis ability. The aim of the present study is to examine the MMP-21 expression in human colorectal cancer and normal colorectal tissue using tissue microarray technique and to determine its association with clinicopathological characteristics and prognostic value.
Materials and Methods Four array blocks including 256 cases of colorectal cancer and adjacent normal tissues were investigated by immunohistochemistry assay. Staining evaluation results were analyzed statistically in relation to various clinicopathological characters and overall survival.
Results High level of MMP-21 expression was detected in colorectal cancer, significantly more than in normal colorectal epithelial cells. In colorectal cancer, MMP-21 was significantly positively correlated with depth of invasion, lymph node metastasis, and distant metastasis. The overall survival rate was significantly lower for patients with MMP-21 positive than those with MMP-21 negative tumors. However, no correlations between MMP-21 expression and patients' age, sex tumor location, or differentiation status were detected.
Conclusion Our findings emphasize the important role of MMP-21 in the invasion and metastasis process in human colorectal cancer. It might also serve as a novel prognostic marker that is independent of, and additive to, the TNM staging system.

Keywords Matrix metalloproteinase-21 · Colorectal cancer · Invasion · Prognosis

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Introduction

Colorectal cancer is one of most common malignant tumors in China and is the fifth most frequent cause of cancer-related death.[1] In 2007, 153,760 cases of colorectal cancer were diagnosed, and 78,700 people died from the disease in China. Despite earlier diagnosis, progressions in radical surgery, radiotherapy, and neoadjuvant chemotherapy, many colorectal cancers remain incurable. In the last decades, the incidence and mortality of colorectal cancer in China have even been increasing due to the early metastases.[2–5] The prognosis of colon cancer was directly correlated with the extent of tumor invasion and metastases.[6] How to diagnose and prevent early tumor metastasis was one of the most important topics in recent tumor studies. Colorectal cancer initiation and progression are associated with stepwise genetic alterations. Molecules involved in cancer recurrence and metastasis might serve

as markers for early detection of metastasis and prognostic judgment.[7,8]

Matrix metalloproteinases (MMPs) are a group of zinc-dependent proteins that are found in the extracellular milieu of various tissues.[9] They are a multigene family of highly homologous enzymes sharing a similar structure, involved in extracellular matrix (ECM) proteins7-10 remodelling processes.[10–13] To date, at least 26 human MMPs have been discovered.[14] Based on sequence homology and substrate specificities, the MMPs can be divided into several distinct subclasses: collagenases, gelatinases, stromelysins, and matrilysins.[15] MMPs are frequently overexpressed in various human cancers and have long been associated with malignancy.[16–18] However, MMPs exhibit considerable promiscuity with respect to their substrates, leading to various redundancies in biological functions.[19] There has been a great deal of interest in the role of MMPs in cancer invasion and metastasis due to their ECM-degrading capacity. To invade and metastasize, tumor cells must infiltrate blood vessels and lymphatics. A substantial subsequent body of work has provided evidence for an association between MMP expression and tumor aggressiveness.[20] In colorectal cancer, 72-kDa gelatinase A (MMP-2), 92-kDa gelatinase B (MMP-9), matrilysin (MMP-7), and stromelysin-3 (MMP-11) were reported to be overexpressed.[20–25] It has also been proven and widely accepted that MMPs expression, such as MMP-2 and MMP-9, were up-regulated in colorectal cancer.[26–32] However, the expression and function of MMP-21, a recently discovered molecule, has not been described in colorectal cancer yet. To date, MMP-21 has been reported up-regulated and related to progression of human malignancy such as ovarian cancer, breast cancer, squamous cell carcinomas and melanoma.[33–36]

In this present study, we investigated the protein expression of MMP-21 and explored the possible relationship to clinical features and overall survival in a large scale of colorectal cancer patients who had not received neoadjuvant chemotherapy.

Materials and Methods

Patients and Specimens

This study was approved by the ethics committee of the Fourth Military Medical University. Fresh colorectal carcinoma specimens and patient-matched adjacent tissues were collected from 256 patients in the Department of Gastrointestinal Surgery of Xijing Hospital at the Fourth Military Medical University (Xi'an, China) between October 2000 and November 2003. Only patients that did not receive neoadjuvant chemotherapy were recruited. Histomorphology of all the primary tumors specimens and regional lymph nodes were confirmed with hematoxylin–eosin staining according to the International Union against Cancer TNM classification by the Department of Pathology, Xijing Hospital at the Fourth Military Medical University (Xi'an, China). Clinical parameters such as gender, age, differentiation status, lymph node metastasis, and TNM stage were collected. Complete follow-up was made available for at least 5 years. In the follow-up period, overall survival was measured from diagnosis to death or last follow-up. Follow-up information of all participants was updated every 3 months by telephone visit and questionnaire letters. Death of participants was ascertained by reporting from the family and verified by review of public records. All specimens were fixed in 10% formalin, embedded in paraffin, and 4-μm serial sections were examined by immunohistochemistry.

Immunohistochemistry Assay

Immunohistochemistry was performed by the avidin–biotin–peroxidase method on all the 256 colorectal cancer tissue specimens. All sections were deparaffinized in xylene and dehydrated through a graduated alcohol series before endogenous peroxidase activity was blocked with 0.5% H_2O_2 in methanol for 10 min. Without washing, sections were incubated with rabbit polyclonal MMP-21 antibody (1:200) in PBS at 4°C overnight in a moist box. Negative controls were performed by replacing the primary antibody with pre-immune rabbit serum. Biotinylated anti-rabbit IgG (1:400, Sigma) was incubated with the sections for 1 h at room temperature and detected with a streptavidin–peroxidase complex. The brown color, indicative of peroxidase activity, was obtained by incubating with 0.1% 3,3-diaminobenzidine (Sigma) in PBS with 0.05% H_2O_2 for 5 min at room temperature. Images were obtained under a light microscope (Olympus BX51, Olympus, Japan) equipped with a DP70 digital camera.

Evaluation of Staining

The MMP-21 staining was viewed separately by two pathologists without knowing the clinical or clinicopathological status of the cases. The expression of MMP-21 on tissue microarray was evaluated by scanning the entire tissue specimen under low-power magnification (×40), and then confirmed under high-power magnification (×200 and ×400). An immunoreactivity score system was applied. The extensional standard: (1) number of positive stained cell ≤5% scored 0; 6~25% scored 1; 26~50% scored 2; 51~75% scored 3; >75% scored 4. (2) Intensity of stain: colorless scored 0; pallide-flavens scored 1; yellow scored 2; brown scored. (3) Multiply (1) and (2). The staining score was stratified as −

(0 score, absent), + (1~4 score, weak), ++ (5~8 score, moderate), and +++ (9~12 score, strong) according to the proportion and intensity of positively stained cancer cells. Specimens will be rescored if the difference of scores from two pathologists was more than 3.[37–39]

Statistical Analysis

Associations between Notch1 expression and categorical variables were analyzed by X^2 test or Fisher's exact test, as appropriate. Associations between MMP-21 expression and clinicopathological characteristics were analyzed by the Mann–Whitney and Kruskal–Wallis tests. Survival curves were estimated using the Kaplan–Meier method and differences in survival distributions were evaluated by the log-rank test. Cox's proportional hazards modeling of factors potentially related to survival was performed in order to identify which factors might have a significant influence on survival, and controlling for age, gender, and differentiation status. Differences with a P value of 0.05 or less were considered to be statistically significant.

Results

Immunohistochemical Detection of MMP-21

In the immunohistochemistry assay, 256 cases of normal and colorectal cancer tissues were investigated. MMP-21 staining mainly located in cytoplasm of tumor cells. The negative staining (−) of MMP-21 were detected in 89 samples of colorectal cancer, the weakly positive staining (+) of MMP-21 was detected in 75 samples, the moderate positive staining (++) of MMP-21 was detected in 58 samples and the strong positive staining (+++) of MMP-21 was detected in 34 samples of colorectal cancer. In contrast, only 5 strong positive stainings (+++) of MMP-21 was detected in normal colorectal tissues, 16 moderate positive stainings (++), 21 weakly positive stainings (+), and 214 negative stainings (−) of MMP-21 were detected. The difference of MMP-21 staining between normal epithelium and colorectal cancer tissues is statistically significant ($P<0.05$).

The Relationship of MMP-21 to Clinicopathological Characteristics

According to the statistical results immunohistochemical assay, the correlation between the MMP-21 expression and clinicopathological characteristics is shown in Table 1. In colorectal cancer samples with different invasion status, the expression of MMP-21 tends to increase from T1 to T4 ($P<0.001$). Although no significant differences were detected between colorectal cancer (CRC) samples with T1 and T2 ($P=0.656$); statistical differences were observed between T2 and T3 ($P=0.005$), T1 and T4 ($P<0.001$), T2 and T4 ($P<0.001$), T3 and T4 ($P=0.017$). Then, we analyzed the relation between MMP-21 expression and node status. As a result, colorectal cancer samples with positive lymph node metastasis tended to have more MMP-21 positive expression than node negative ones ($P<0.001$). As far as distant metastasis was concerned, colorectal cancer samples with distant metastasis had more positive staining of MMP-21 than M0 ones. MMP-21 was also detected to be increased with TNM stage. The expression of MMP-21 was not correlated to patient's gender, age, tumor location, or differentiation status.

The Relationship of MMP-21 to Overall Survival

The mean follow-up time of patients in the study cohort was 72.8 months with median follow-up time of 64.2 months, and the 5-year survival rate of 192 patients was 54.7%. Kaplan–Meier postoperative survival curve was used to evaluate the overall survival rate of patients with colorectal cancer and MMP-21 expression (Fig. 1, log-rank test, $P=0.001$). The postoperative median overall survival time of all patients with colorectal cancer cannot be estimated due to good overall survival. The median survival time of patients with strong positive (+++) and moderate positive (++) expression of MMP-21 was 30 months (95% CI, 18–42) and 43 months (95% CI, 35–51; log-rank test, $P<0.05$). The median survival time of patients with weak positive (+) and negative expression of MMP-21 cannot be estimated either. Unadjusted hazard ratio (HR) set 1.00 as reference in MMP-21 negative (−) expression group, the unadjusted HR of weak positive (+), moderate positive (++) and strong positive (+++) groups were 3.15 (95% CI, 1.61–6.18; $P<0.05$), 6.13 (95% CI, 3.09–12.15; $P<0.001$) and 7.71 (95% CI, 5.10–18.48; $P<0.001$), respectively. Moreover, differentiation status (log-rank test, $P<0.001$), lymph node metastasis (log-rank test, $P<0.001$) and TNM stage (log-rank test, $P<0.001$) were also proved to be prognostic factors for overall survival of patients with colorectal cancer. Patients with positive lymph node metastasis or vascular invasion had shorter overall survival. However, sex, age, differentiation status or vascular invasion had no prognostic value on overall survival of patients with colorectal cancer. Unadjusted HR was shown in Table 2.

Cox proportional hazards model adjusted for age, gender, differentiation, tumor location and TNM stage were shown in Table 2. In multivariate analysis, TNM stage and MMP-21 expression were two independent prognostic factors. Adjusted HR was 1.00 (as a reference) in MMP-21 negative (−) expression group, the adjusted HR of weak

Table 1 Statistical results of immunohistochemistry assay

	n	MMP-21				*P*
		–	+	++	+++	
Total	256	89	75	58	34	
Gender						0.728[a]
Men	142	51	41	31	19	
Women	114	38	34	27	15	
Age						0.656[a]
<60	101	30	34	24	13	
≥60	155	59	41	34	21	
Tumor location						0.191[b]
Right colon	76	29	22	16	9	
Left colon	68	27	20	14	7	
Rectum	112	33	33	28	18	
Histology						0.616[b]
Poorly differentiated	79	30	21	18	10	
Moderately differentiated	119	42	36	26	15	
Well-differentiated	58	17	18	14	9	
Invasive depth						<0.001[b]
T1	37	21	8	5	3	
T2	71	39	11	14	7	
T3	93	24	35	21	13	
T4	55	5	21	18	11	
Lymph node status						<0.001[a]
N0	134	59	34	29	12	
N1	122	30	41	29	22	
Distant metastasis						<0.001[a]
M0	233	86	70	54	23	
M1-3	23	3	5	4	11	
TNM stage						<0.001[a]
I	76	38	18	16	4	
II	55	21	14	13	7	
III	102	27	38	25	12	
IV	23	3	5	4	11	

[a] *P* value when expression levels were compared using Mann–Whitney test

[b] *P* value when expression levels were compared using Kruskal–Wallis test

positive (+), moderate positive (++), and strong positive (+++) groups were 3.41, 3.58, and 6.12, respectively. Thus, MMP-21 could be an independent predictor of survival for patients with colorectal cancer. In addition, there was no significant correlation between age, gender, or differentiation distribution and survival in the patients.

Discussion

Colorectal cancer is one of the most common malignant tumors all over the world. One of the greatest challenges in colorectal cancer management is to accurately predict outcome for each patient so that we can determine who will benefit from adjuvant therapy. To achieve this, presently, people rely heavily on traditional pathologic variables, such as tumor size, lymph node status, and tumor grade. Currently, TNM and Dukes' staging system of tumors is the gold standard for determining prognosis in patients with colorectal cancer; whereas the staging system, relying on the extent of disease at the time of diagnosis, is less informative for each individual patient. Patients with similar stages of disease even showed a big discrepancy in survival. Although several new molecular prognostic factors such as P53 and KRAS mutations are being evaluated in the hope that they may contribute to better assessment of the survival probability. It is still not possible to accurately predict the prognosis of patients following surgery and consequently to make tailored treatment for each individual patient.[40]

Neoadjuvant chemotherapy prior to surgery has been proven to alter MMPs expression such as MMP-9.[41,42] It

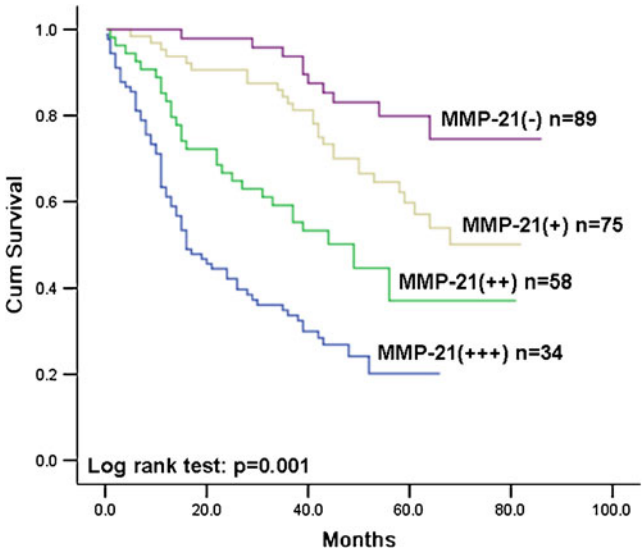

Fig. 1 Kaplan–Meier postoperative survival curve for patterns of patients with gastric cancer and MMP-21 expression

might due to the effects of 5-fluorouracil on NF-κB activity which can regulate MMPs in human malignancy.[43–45] Neoadjuvant chemotherapy prior to surgery can alter not only MMPs expression but also postoperative survival time, thus inevitably raise a higher possibility to generate false-negative results. It has been proved that, compared with patients who did not receive 5-Fu based chemotherapy, patients treated with 5-Fu would lose the prognostic value of MMP-9.[46] Therefore, only patients who had not received neoadjuvant chemotherapy were recruited in our present study in order to diminish the influence of the neoadjuvant on MMPs and survival of patients.

The primary aim of this study is to determine the MMP-21 expression and the relation to clinicopathological characteristics and prognosis of patients. As a result, we confirmed a significant elevated expression level of MMP-21 in this cohort of colorectal cancer compared to adjacent normal tissues. Moreover, MMP-21 was highly expressed with depth of invasion, especially in T4 carcinomas, since statistical differences were detected between T1/T2/T3 and T4 tumors, suggesting the role of the MMP-21 involved in the breakdown the ECM, which is important for the invasion of solid tumor. As far as lymph node status and distant metastasis were concerned, both node-positive and distant-metastasis-positive CRC samples tend to show elevated MMP-21 expression. However, its expression

Table 2 Association of molecular and clinical factors with overall survival of patients with gastric cancer

	Unadjusted HR[a] (95% CI)	*P*	Adjusted HR[b] (95% CI)	*P*
MMP-21				
Negative	–		–	
Weak positive	3.15(1.61–6.18)	0.001	3.41(1.73–6.73)	<0.001
Moderate positive	6.13(3.09–12.15)	<0.001	5.44(2.71–10.93)	<0.001
Strong positive	7.71(5.10–18.48)	<0.001	10.02(5.23–19.20)	<0.001
Sex				
Female	–		–	
Male	1.17 (0.68–2.02)	0.562	1.18 (0.68–2.06)	0.542
Age				
≤60	–		–	
>60	1.04 (0.68–1.58)	0.867	1.23 (0.80–1.90)	0.353
Differentiation status				
Well	–		–	
Moderate	1.22(0.70–2.14)	0.476	1.36(0.68–2.72)	0.381
Poor	2.22(1.24–3.98)	0.007	1.81(0.94–3.46)	0.047
Vascular invasion				
Absent	–		–	
Present	2.20(0.80–6.03)	0.125	1.36(0.44–3.18)	0.587
Node metastasis				
Absent	–		–	
Present	2.47 (1.61–3.78)	<0.001	3.14 (1.26–7.87)	0.015
TNM stage				
I	–		–	
II	1.90(1.03–3.52)	0.042	1.83(0.94–3.57)	0.077
III	2.45 (1.41–4.27)	0.002	2.35 (1.36–3.98)	0.001
IV	3.13 (1.56–6.30)	<0.001	3.58 (1.46–6.85)	<0.001

HR hazard ratio, *95% CI* 95% confidence interval

[a] Hazard ratios in univariate models

[b] Hazard ratios in multivariable models

was not correlated with age, gender, tumor location, or tumor differentiation. In this perspective, MMP-21 expression may increase as tumor invades, suggesting the possible role of MMP-21 in the invasion and metastasis process of CRC. Kaplan–Meier analysis of the survival curves showed a significantly worse overall survival for patients whose tumors had high MMP-21 levels (log-rank test $P=0.001$), indicating that high MMP-21 tumor protein level is a marker of poor prognosis for patients with colorectal cancer. Cox proportional hazards model adjusted for age, gender, tumor location, differentiation status and TNM stage showed the same trend as Kaplan–Meier postoperative survival curve. Moreover, multivariate analysis showed MMP-21 expression to be a marker of worse outcome independent of the known clinical prognostic indicators such as TNM stage. These data suggested that MMP-21 expression was correlated with worse outcome and might be an independent prognostic factor for patients with colorectal cancer. It could constitute a useful prognostic marker additive to the TNM staging system for these patients, identifying patients that are more likely to have disease recurrence and are, thus, good candidates to receive an aggressive adjuvant chemotherapeutic treatment.

Our study provides first evidence that MMP-21 expression is elevated in primary CRC and related to tumor invasion, metastasis, and prognosis. Although prospective studies will be needed to determine the prognostic utility of MMP-21 in malignant tumors, our findings support the notion that MMP-21 may be a molecule involved in tumor invasion and metastasis and indicated that MMP-21 was an independent prognostic factor for patients with colorectal cancer. MMP-21 might also serve as a potential target for anti-metastatic therapy via selective MMP inhibition.

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ORIGINAL ARTICLE

One Hundred and Two Consecutive Robotic-Assisted Minimally Invasive Colectomies—An Outcome and Technical Update

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Abstract
Background The objective of this study was to review 102 consecutive robotic colectomies at our institution. We evaluated the 8-year experience of one surgeon (DLC) in Peoria, IL using the da Vinci system.
Methods An IRB-approved retrospective review was performed. Results were compared with the literature. Changes in technique over the years were evaluated.
Results One hundred and two robotic colectomies, right (59) and sigmoid (43), were performed. Mean age is 63.5 years and mean BMI 27.4 kg/m². Preoperative indications are polyps (53), diverticular disease (27), cancer (19), and carcinoid (3). Mean total case time (TCT) for all cases is 219.6±45.1 (50–380) min, and mean robot operating time (ROT) is 126.6±41.6 (12–306) min. Operative times for Right: Port setup time (PST) 32.4±10.5 (20–64) min, ROT 145.2±39.6 (53–306) min, TCT 212.3±46.4 (50–380) min; times for sigmoid: PST 31.2±9.6 (10–57) min, ROT 101.2±29.2 (12–165) min, TCT 229.7±41.6 (147–323) min. Median length of stay for all patients is 3 (2–27) days. The overall complication rate is 18.6%, the overall conversion rate 8.8%, and the anastomotic leak rate is 0.98%. Residents PGY 1–5 participated in 61 cases (59.8%).
Conclusion We report our updated procedural sequence and technical alterations. Experience has allowed residents to evolve to be primary surgeons. We add our results to the current robotic literature.

Keywords Robotic surgery · Minimally invasive surgery · Colectomy · Resident education

Introduction

The ability to perform an operation from a remote location, desired by the Department of Defense, ultimately led to the realization of robotic surgery. The da Vinci system (Initiative Surgical, INC., Sunnyvale, CA) was approved for general surgery by the Food and Drug Administration in 2000. Since that time, robotic surgery, though far from the standard of care, is becoming more frequently used by surgeons of a variety of specialties for an increasing list of procedures.

The first laparoscopic-assisted colectomies were reported in 1991.[1] At around the same time, laparoscopic cholecystectomy became the treatment of choice for gallstone disease.[2] Laparoscopic surgery, now considered the standard of care for several intra-abdominal procedures,[2–4] offers several well-known advantages to the patient. For the surgeon, however, it provides several challenges as well. Several disadvantages to the surgeon are inherent to laparoscopic surgery. Replacement of the surgeon's wrist with a laparoscopic instrument restricts the natural movements from being available. In many instances, laparoscopy provides better visualization of the surgical field when compared with the open procedure. At the same time, visualization is reduced from three to two dimensions and is under the control of an assistant running the camera. Much

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of the excitement associated with robotic surgery is related to the restoration of these abilities. Laparoscopic surgical instruments allow the following motions: (1) in/out, (2) pitch (up/down), (3) yaw (left /right), (4) rotation, (5) grasp. Robotic surgery adds two additional motions: (6) internal pitch and (7) internal yaw at the instrument tip. Thus, all seven natural motions available to the human wrist are again restored to the operating surgeon. The da Vinci system provides a three-dimensional operating field view, which can be magnified up to ten-fold, while at the same time restoring control of the visual field to the operating surgeon. The surgical console allows the surgeon to remain seated in a comfortable and ergonomically friendly position. Additional advantages include motion scaling and tremor elimination which may prove to be important during procedures such as total mesenteric excision which require small movement within a narrow and difficult to visualize space.

We have previously demonstrated that robotic colectomy is safe, feasible, and reproducible using a defined technique.[5] As our experience has grown, we continue to improve upon this technique. We report improvements in port placement and operative sequence. Standardization and further refining of the techniques used to perform right and sigmoid colectomies robotically have allowed for consistent operative times, more reproducible results, and increased resident involvement.

The purpose of the study was to review 102 consecutive robotic colectomies at our institution and add to and compare our results with the current reported literature. We also demonstrate that significant resident participation in these procedures is safe and feasible. We evaluated the 8-year experience (2002–2009) of one minimally invasive surgery (MIS) fellowship trained surgeon in Peoria, IL using the da Vinci Telerobotic system. Colon procedures are the 6th most commonly performed procedure of the senior author.

Material and Methods

An IRB-approved retrospective review of prospectively collected data from 2002 to 2009 representing 102 robotic colon operations was performed. Operations were performed by one MIS fellowship trained surgeon with resident assistance. The patients were given the choice of the hospital without knowing which hospital offered the da Vinci system. If one of the hospitals with the Robotic system was chosen, the patient was offered a laparoscopic or robotic approach. Pertinent risks and benefits were discussed with patients, and written informed consent was obtained. Data analyzed were: procedure performed, indication for surgery, gender, age, body mass index (BMI), estimated blood loss (EBL), port setup time (PST), robot operating time (ROT), total case time (TCT), length of stay (LOS), complications, conversions, and resident involvement. Port setup time was defined as the time from the first skin incision until the surgeon sat down at the console to begin the robotic portion of the procedure. Robotic operative time was defined as the time of the surgeon's first use of the robot until it was disengaged from the trocars and the patient. The total case time was the time from skin incision to skin closure and included all involved procedures, robotic or laparoscopic. Indications for surgery included diverticular disease, polyps, carcinoid, and cancer. Statistical analysis using the ANOVA test was performed. The changes in technique and operative approach for right and sigmoid colectomies over the years were evaluated. The results were compared with the current literature.

The da Vinci System

The da Vinci system remained unchanged from previous publications as described by Rawlings et al.[5]

Right Colectomy

Robotic right colectomy is performed with the patient in the supine position. The patient is placed on a beanbag, and the bag wraps the left arm. The chest and legs are secured to the table with conventional straps on the legs and heavy tape at the tibial area and the level of the clavicles. These measures are essential given the positioning necessary to carry out the procedure. The operative suite is arranged as shown in Fig. 1. Once pneumoperitoneum is established, trocars are placed as depicted in Fig. 2. The camera is placed through the 12-mm periumbilical trocar. With the omentum reflected cranially, the planned point of division of the transverse colon and mesocolon are marked with endoclips based on the right branch of the middle colic artery. The terminal ileum is also run for 20–30 cm to ensure it is not fixed in the pelvis, as it must reach the transverse colon for the coloenteric anastomosis. The table is then tilted steeply to the left and in slight Trendelenburg position to allow the small bowel to fall out of the visual field and to keep the omentum above the transverse colon. The robot is positioned over the right upper quadrant (see arrow Fig. 2), and the camera and instruments are docked. The robot's right arm is placed through the 5- or 8-mm epigastric trocar, and the left arm is placed through the 5- or 8-mm right lower quadrant trocar. A 5-mm trocar is inserted in the left lower quadrant for use by an assistant using a laparoscopic instrument to retract and expose the ileocolic vascular pedicle. A grasper placed through the 12-mm left lateral abdominal wall port can be used to hold the transverse mesocolon cephalad and out of the way.

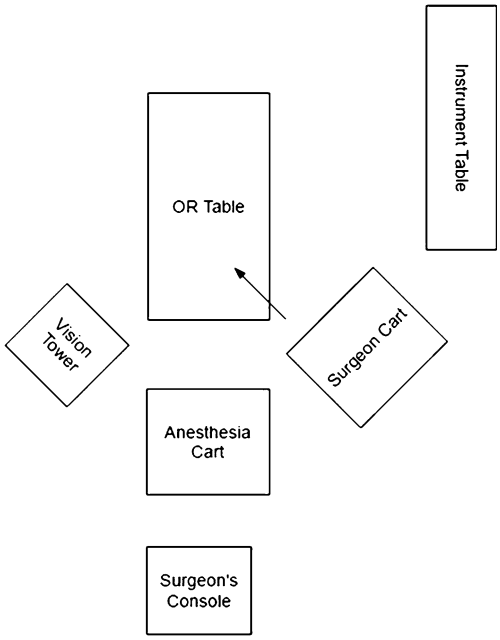

Fig. 1 Da Vinci OR setup: right colectomy

We proceed with a medial to lateral dissection by first encircling and then dividing the ileocolic vascular pedicle with a vascular load laparoscopic stapler at the level of the duodenum. The right mesocolon is then mobilized from Gerota's fascia. If the appropriate plane is difficult to identify, the cecum can be mobilized lateral to medial until the ureter is seen. Then, returning to the medial approach, the plane is easier to see. One must not mobilize the right colon, only the cecum, because the colon will later fall medially and be in the way during medial mobilization and the anastomosis. After identification of the ureter, the ileal mesentery is divided using a harmonic energy device to a point 10 cm proximal to the ileocecal valve. Once the entire right colon is mobilized out to the abdominal wall and around to the duodenal sweep, attention is directed to the transverse mesocolon. The previously incised or clipped line on the mesocolon is found, and the right branch of the middle colic artery is identified. Clips and vascular staplers are used as needed to ligate this vessel. Previously, we would divide the entire mesocolon up to the colon and dissect all the tissue off the pancreatic head and then divide the colon. We have subsequently started encircling and dividing the transverse colon at its planned point of division immediately after clipping of the right branch of middle colic artery. We have learned that this allows us to distract the two cut ends of the colon to better see the transverse mesocolon, gastrocolic ligament, and tissue on the pancreatic head which must all be dissected and taken with the specimen. The mesocolon is then divided with a harmonic device down to the pancreas. The mesocolon is then taken off the pancreas and vessels controlled. The gastrocolic ligament is divided as it is followed to the greater curve of the stomach. The gastroepiploic vessels can be taken off the stomach or preserved based on the surgeons preference and the indication for resection. Following the stomach to the patient's right will lead back to the previously dissected tissue at the duodenal sweep. The ileum is then divided intracorporeally with a laparoscopic stapler. At this point, the right colon remains attached to its lateral peritoneal attachments helping to keep it retracted laterally.

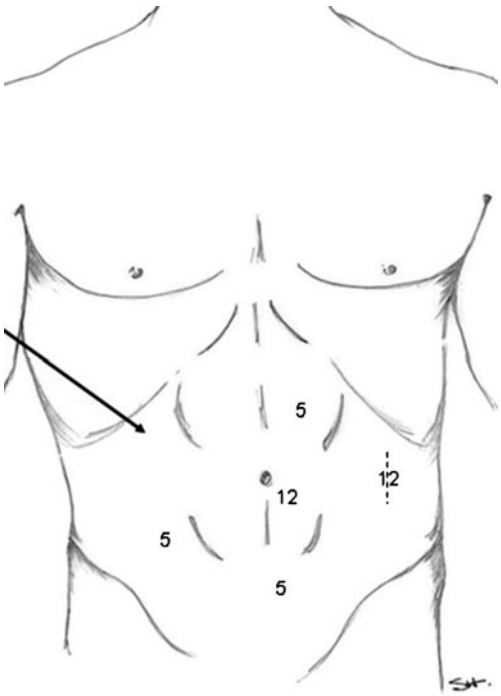

Fig. 2 Trocar positioning robotic right colectomy

An intracorporeal anastomosis is then created in an isoperistaltic side-to-side fashion between the ileum and transverse colon. The ileum is joined to the transverse colon 6 cm from the end of the ileum using a 30-cm 2–0 silk suture on a Keith needle. This needle is then externalized in the right upper quadrant and clamped externally for retraction (Fig 3). A harmonic energy device is then used to create enterotomies, through which the ends of an endoscopic linear cutting stapler are inserted and fired. This stapler is brought through the left lateral 12 mm trocar. The stapler defect in the bowel is closed with a running 2–0 absorbable braided suture. The mesenteric defect is then closed with absorbable suture. The retracting 2–0 silk suture is divided, and the lateral attachments of the right colon are taken down with a harmonic device or cautery. The specimen is extracted through the left lateral 12-mm trocar site after extending it to approximately 4 cm. The wound is protected by using a specimen bag before extraction. Standard closure techniques are then followed.

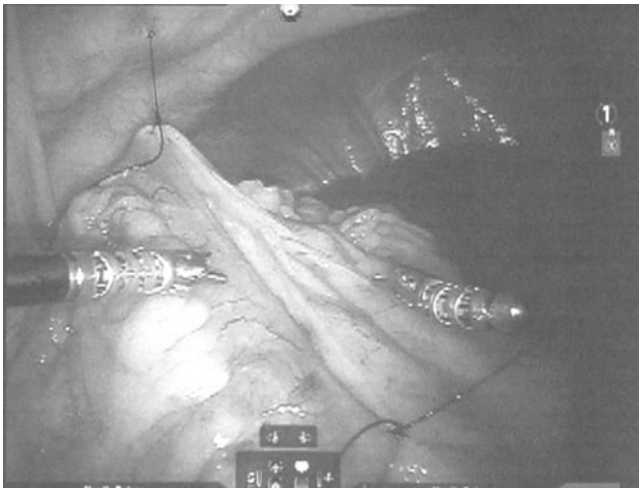

Fig. 3 Bowel alignment for intracorporeal ileocolic anastomosis

Sigmoid Colectomy

Robotic sigmoid colectomy is performed with the patient in a supine modified lithotomy position, in which the anterior thighs are in the same plane as the abdominal wall. The patient is placed on a beanbag so that the bag can wrap the right arm and the chest is secured to the table with heavy tape at the clavicles (Fig 4). The operative suite is arranged as shown in Fig. 5. Trocars are placed as seen in Fig. 6 after pneumoperitoneum is obtained. The procedure is begun with the patient in a steep right-sided tilt and reverse Trendelenburg position. The robot is brought in from the left side of the patient (see arrow a, Fig. 6). The right arm and its trocar are slipped through the suprapubic 12 mm port or the arm can be docked to the left lateral abdominal wall 5 mm robot port. The left arm is docked to the epigastric port. A harmonic energy device is used in the left arm and a grasper in the right. The splenic flexure is taken down by dividing the gastrocolic ligament then elevating

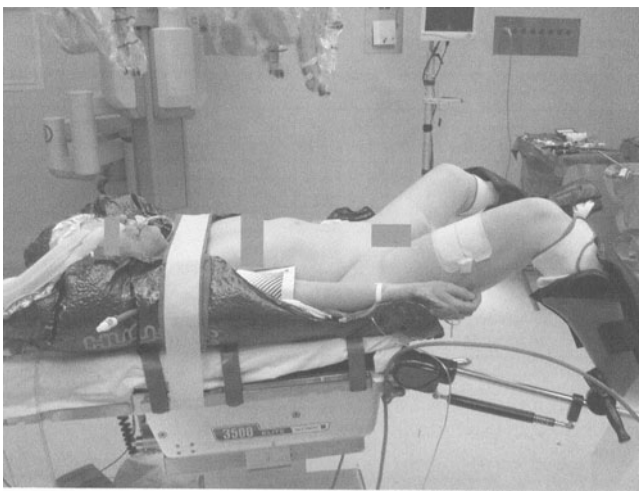

Fig. 4 Patient positioning on or table: sigmoid colectomy

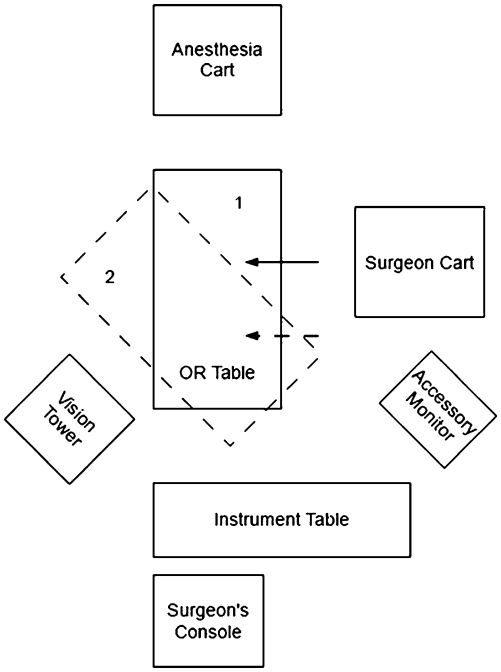

Fig. 5 Da Vinci OR setup: sigmoid colectomy

the mesocolon off of Gerota's fascia. Downward and medial retraction by the assistant from the right sided trocars is invaluable. Electrocautery can be used for the latter portion of this mobilization over Gerota's fascia, but harmonic energy is particularly helpful with the thick and often vascular gastrocolic ligament. Visualization of the ligament of Treitz through the mesentery marks the medial

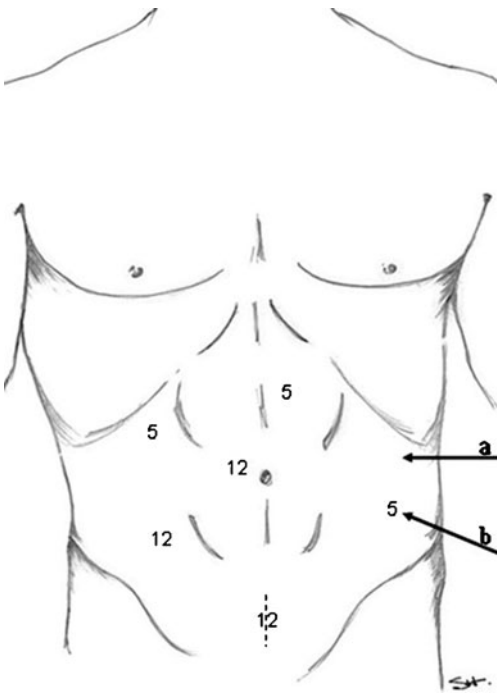

Fig. 6 Trocar positioning robotic sigmoid colectomy

extent of proximal mobilization. The inferior mesenteric vein is selectively taken for benign diagnoses and routinely taken for malignant. Because left ureter visualization medially is the goal all the way to the pelvic brim, changing table position is required. The robot is disengaged and drawn back from the table. The patient is placed in Trendelenberg position, and the robot is brought in from the left hip (see arrow b, Fig. 6). The right arm and its trocar are slipped through the right lower quadrant 12 mm port and cautery or harmonic energy device is attached. The left arm is connected to the left lateral abdominal wall robot trocar, and a grasper is inserted. The sigmoid colon is elevated, and the inferior mesenteric vascular pedicle is demonstrated. The peritoneum on the right side of the rectosigomid colon is scored at its base, and the inferior mesenteric artery is isolated. The rectosigmoid colon is then mobilized circumferentially down to the desired level on the rectum while visualizing both ureters. The harmonic energy device is used to divide the mesorectum.

At this point, the robot is disengaged and endoscopic staplers are used to divide the inferior mesenteric artery and the rectum. The suprapubic port is extended to accommodate externalization of the specimen through a protecting bag. After proximal division of the colon and resection of the specimen, the anvil of an end-to-end anastomotic stapler is secured into the end of the colon. The colon is returned to the abdomen, and the fascia is closed to allow for reestablishment of the pneumoperitoneum. The stapler is then inserted transanally and attached to the anvil and fired. We routinely test our anastomoses with insufflation. Standard closure techniques are then followed.

Postoperative care is similar to that in patients undergoing laparoscopic colectomy, with an emphasis on quicker recovery times. Clear liquids are offered the day of surgery and early ambulation is encouraged. Patient-controlled analgesia is employed until patients are tolerating diet and oral medicines. Epidurals are not used. Criteria for discharge include tolerance of liquids, ability to void, adequate pain control with oral analgesics, and evidence of bowel function. Follow-up visits are scheduled within 1 to 2 weeks from the day of discharge.

Results

One hundred and two colon cases, right (59) and sigmoid (43), were performed in 49 males and 53 females for preoperative indications of diverticular disease (27), polyps (53), cancer (19), and carcinoid (3). Mean operative times for all cases were PST 31.9±10.1 (10–64) min, ROT 126.6±41.6 (12–306) min, and TCT 219.6±45.1 (50–380) min. EBL was 66.6±71.3 (15–500) ml, BMI 27.4±4.3 (17.0–40.5) kg/m², and median LOS 3.0 (2–27) days. Fourteen different types of complications occurred (Table 1). Nine cases had a change in operative approach—four were concluded laparoscopically and five were converted to open for a total conversion rate of 8.8%. Residents participated in 61 cases (59.8%). Mean operative times for all right colectomy cases were PST 32.4±10.5 (20–64) min, ROT 145.2±39.6 (53–306) min, and TCT 212.3±46.4 (50–380) min. The mean age for this group was 66.7±11.3 (31–86) years, BMI 27.5±4.2 (17–36.8) kg/m², EBL 58.6±80.8 (15–500) ml, and median LOS 3.0 (2–27) days. Resident participated in 32 cases (59.2 %). Mean operative times for all sigmoid colectomy cases were PST 31.2±9.6 (10–57) min, ROT 101.2±29.2 (12–165) min, and TCT 229.7±41.6 (147–323) min. The mean age for this group was 59.1±15.4 (22–86) years, BMI 27.2±4.6 (17-F.5) kg/m², EBL 77.6±54.7 (15–250) ml, and median LOS 3.0 (2–27) days. Residents participated in 29 cases (67.4%).

Complications and Conversions

Nineteen patients (18.6%) experienced complications. Complications are listed in Table 1. There we no complications attributable to the robotic device or approach. Comparison of our conversion and complication rate to the current literature is difficult for several reasons. Many groups report only a few colon procedures as a part of a larger series of general surgical procedures. It also varies as to what is included as a complication. In review of Table 2, reported complication rates ranged from 0% to 33.3%. Review of large series reporting 50 or greater robotic colon resections reveals complication rates of 7.5,[19] 10.7,[7] 14.0,[9]

Table 1 Complications: right and sigmoid colectomy

Complication	Number
Anastomotic leak	1
Ileus	7
Cecal injury	1
Transverse colon injury	1
Internal hernia	1
Pelvic abscess	1
Small bowel obstruction	1
Patient slid off operating table	1
Rectal bleeding	1
Abdominal wall hematoma	1
Urinary retention	3
Left hip paresthesia	1
Prolonged intubation	1
Anemia	2

Table 2 Robotic colectomy series

Author	Year	Number	Total Case Time	Complications		Conversion		Kind of conversion	
			(min)	(*n*)	Rate (%)	(*n*)	Rate (%)	Laparotomy (*n*)	Laparoscopy (*n*)
Crawford	2009	102	219.6 (50–380)	19	18.6	9	8.8	5	4
Luca[6]	2009	55	290 (164–487)	12	21.8	0	0		
Baik[7]	2009	56	190.1 (120.0–315.0)	6	10.7	0	0		
Choi[8]	2009	13	260.8 (210–390)	3	23.1	0	0		
Spinoglio[9]	2008	50	383.8	7	14.0	2	4.0	1	1
Baik[10]	2008	18	217.1 (149–315)	4	22.2	0	0		
Crawford[11]	2008	70	225 (147–380)	21	30.0	8	11.4	5	3
Baik[12]	2007	9	220.8 (153–315)	3	33.3	0	0		
Hellan[13]	2007	39	285 (180–540)	5	12.8	1	2.6	1	
DeNoto[14]	2006	11	197 (145–345)	0	0	1	9.1	0	1
Crawford[5]	2006	30	226 (90–340)	6	20.0	2	6.7	2	0
Ayav[15]	2005	6	172 (45–280)	1	16.7	1	16.7	1	
Braumann[16]	2005	5	201 (80–300)	0	0	2	40.0	2	0
Anvari[17]	2005	6	109 (90–160)	0	0	0	0		
Woeste[18]	2004	4	236.7	1	25.0	1	25.0	1	0
D'Annibale[19]	2004	53	240	4	7.5	5	9.4	0	5
Anvari[20]	2004	10	155.3	0	0	0	0		
Ayav[21]	2004	5	265 (180–240)	1	20.0	1	20.0	1	0
Hanly[22]	2004	35	177	–	–	5	14.3	5	0
Hubens[23]	2004	7	NA	2	28.5	0	0		
Ewing[24]	2004	12	248 (180–350)			0	0		
Delaney[25]	2003	6	216.5 (170–274)	0	0	1	16.7	0	1
Giulianotti[26]	2003	16	211 (90–360)	1	6.3	0	0		
Vibert[27]	2003	3	380 (330–450)	1	33.3	0	0		
Weber[28]	2002	2	284 (228–340)	0	0	0	0		
Hashizume[29]	2002	3	260 (180–335)	–	–	0	0		

and 21.8.[6] Our complication rate of 18.6 lies at the higher end of this range. We feel this is due to the low threshold of what we considered a complication. Notably, only one patient (0.98%) experienced an anastomotic leak in our series. Review of the other large series reveals a rate of anastomotic leak of 0,[6,19] 4%,[9] and 12.7%.[6] Exactly what was considered a "leak" varied within the papers reviewed most leaks were recognized clinically while some reported diagnosis with lower GI contrast study.[6] A total of nine cases (8.8%) required conversion in our series, five being converted to an open approach and four being converted to laparoscopic. Our reasons for conversion included dense adhesions, colonic ischemia, venous bleeding, difficulty finding the tumor, and stapler malfunction. Conversion rates in series of 50 or more robotic colectomies were 0 in two studies,[7,9] two out of 50 (4%) with one conversion to open and one conversion to a laparoscopic procedure,[9] and five of 53 (9.4%) all converted to laparoscopic procedures.[19] Our conversion rate positions us at the higher end of the range of conversions compared to other large series. Continued scrutiny of our data as our series grows will hopefully reveals risk factors for conversion.

Resident Involvement

Resident involvement in robotic surgery plays an important role at our institution. After several years of refining his robotic colectomy technique, the senior author (DLC) developed a safe and reliable technique that he was comfortable teaching the residents. Residents are allowed to participate in robotic colectomies starting their first year of residency. As expected, resident participation increases with increasing PGY level of the resident (Fig. 7). If we look closer at what each level of resident is doing during the cases, we see that PGY 1 residents are immediately involved in assisting with the robotic cases, usually retracting using laparoscopic instruments. This is seen

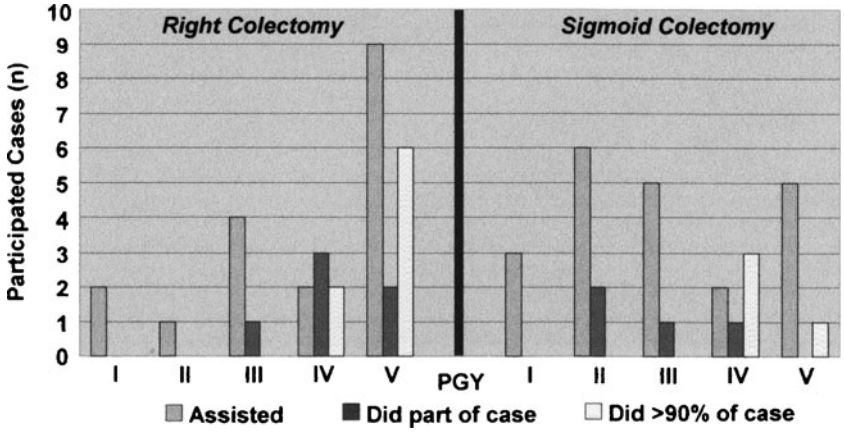

Fig. 7 Resident participation PGY 1–5: right and sigmoid colectomy

more so in the sigmoid colectomies when compared to right colectomies. Beginning in the second year, residents are allowed to perform part of the case at the surgeons console under instruction of the senior author. Fourth and fifth year residents will complete the entire robotic portion of the case, while the senior author remains as assistant at the operating table.

Discussion

The mean port setup times for the right and sigmoid colectomy groups were similar, and no statistically significant difference was found (right colectomy 32.4 ±10.5 min vs. sigmoid colectomy 31.2±9.6 min p=0.55 CI −2.85 to 5.24). Many series report "docking time" as how long it takes to connect the robot to the patient. The manufacturer comments on how much faster the new SI is to dock compared to the older model and we agree with them. However, our measure of PST includes docking time and all adhesiolysis needed to free the abdomen of adhesions in preparation for surgery. Because we are approaching more patients with complex surgical histories robotically and we teach residents to use the system, we do not expect our PST to fall much more, if any, in the coming years. A statistically significant difference in mean robot operative time was found when comparing right and sigmoid colectomy (right colectomy 145.2± 39.6 min vs. sigmoidetomy 101.2±29.2 min p<0.0001 CI 29.9 to 58.2). Much of this is attributed to our current practice of performing the ileocolic anastomosis intracorporeally. During sigmoid colectomy, the robot is used only for mobilization of the colon then an end-to-end anastomosis is performed laparoscopically after specimen extraction, thus shortening total robotic operative time. In comparing the mean total case times for right and sigmoid colectomy, no statistical significance was found (right colectomy 212.3±46.4 min vs. sigmoidectomy 229.7±41.6 min p=0.05 CI −35.03 to 0.33). Our mean total case time for all colectomies was 219.6 min. This compares favorably with the current literature (Table 2), [6,30] from which a mean total case time of 236.4 min (50–540) was calculated. When comparing our mean operative time for colectomy (219.6 min) to the mean of the four other groups reporting 50 or more robotic operations in a series (275.9 min) our time again compares favorably. D'Annible et al.[19] report a mean operative time of 240±61 min for a series of 53 robotic colorectal procedures. Their technique for robotic right colectomy and low anterior resection (LAR) are similar to our own, as they also perform an intracorporeal-stapled anastomosis for LAR procedures. However, right colectomy ileocolic anastomoses are performed by hand extracorporeally. It is also difficult to compare our mean operative time to that reported by D'Annible et al. because they include several other colorectal procedures in their reported mean operative time. Luca et al.[6] report a mean operative time for robotic sigmoid and rectal cancer resections of 290±69 min. Similar to the report by D'Annible et al., Luca et al. also include both right, sigmoid, LAR, and Miles' procedures, the latter two of which require total mesorectal excision. This complex pelvic dissection obviously requires additional time. The additional time needed for completion of a TME is exemplified in the subgroup analysis done by Spinoglio et al.[9] who reported 50 robotic colorectal operations with mean operative times classified by the first 20 cases vs. last 30 cases for three different operations (right hemicolectomy, 368 min for the first cases vs. 267 min for the last; sigmoid hemicolectomy, 425 min for the first cases vs. 345 min for the last; rectal resection with total mesorectal excision, 457 min for the first cases vs. 404 min for the last). They also demonstrate quite well the impact that experience and stepwise reproducible technique have on reducing operative times. Finally, Baik et al.[7] reported 56 patients undergoing robotic low anterior resections with a mean operative time of 191.45±45.0 min; however, a closer look reveals that

their entire left colon mobilization is done entirely laparoscopically with only the TME portion done robotically.

In our series, one must consider that a significant amount of the total operative time taken was taken up by residents of varying PGY levels being instructed by the senior surgeon. Thus, once comfortable with the robotic procedure, the total operative time in a non-training environment would be expected to be somewhat shorter. This is an important consideration when comparing our total robotic operative times to reported operative times for non-teaching centers. Unfortunately, resident involvement is not commented upon in any of the literature available for comparison.

The minimally invasive surgical literature repeatedly compares robotics to laparoscopy. However, one must consider that the majority of colon surgery is still done open. A study from 2011 done by Robinson et al. demonstrated this fact. Their study included 240,446 colon resections performed between 2005 and 2007. During that time, laparoscopic colon resections for colon cancer increased by only 2% (6.7% from 4.7%). Laparoscopic resections for benign colon diseases increased only 1.8% (27.4% from 25.2%).[30] Therefore, we felt that it would be useful for the majority of surgeons in the USA to see a comparison of robotic data to open colon surgery. Some might argue that it is a considerable leap for those performing open colectomies to perform robotic colectomies. However, that is the progression that occurred in the field of urology. The laparoscopic procedure was essentially bypassed due to the fact that it was so technically challenging. In fact, laparoscopic prostatectomy was only performed in a few select centers due to this. At the present time, more robotic prostatectomies have been performed than any single robotic procedure.[31] Table 3[32–35] compares our robotic colectomy data to recently published papers that included the results of large series of open colectomies. In comparing our robotic data to the open colectomy data, two of the open series reported total operative time, 178±80 and 152.1±83 min. This is shorter than our total mean total case time of 219.6±45.1 min. This was expected given the time for docking the robot, 31.9±10.1 min in our series. However, our robotic operative of 126.6±41.6 was shorter than that reported for the open series. Our complication rate of 18.6% and mortality of 0% were lower than the open data in any of the open series. In 2007, we published our costs data for robotic colon surgery.[36] Total hospital costs were $9,255 for robotic colectomies, which is well within the range of the open series listed in Table 3, ranging from $8,076 to $34,179, the latter of which was extrapolated from the national inpatient survey of 95,627 open colectomies. By this simplistic comparison, robotic colectomy takes 30–60 min longer, has a shorter length of stay, and equivalent if not superior morbidity, mortality, and cost when compared to its open counterpart. We wonder why

Table 3 Comparison of open vs. Robotic colectomy

Name	Year	Study type	Database	Number of open pts.	% Open pts. of database	Mean age	Operations	Oper. time (min)	Complications (%)	Mortality (%)	LOS (Days)	Hosp. cost
Crawford	2011	Retrospective		N/A[a]			RRSC	219.6±45.1	18.6	0	3.0 (2–27)	9,255[b]
Bilimoria[32]	2008	Retrospective	A	2,222	72.6	68 (57–78)	EOC	152.1±83.0	21.7	1.8	8.7	
Delaney[33]	2008	Retrospective	B	21,689	66.3	64.2±13.9	EOC+	178±80	31.8		8.1	8,076
Hinojosa[34]	2007	Retrospective	C	9511	89.7		EOC++	N/R	Benign 25.4	Benign 0.6	Benign 7.2±7.6	Benign 15,248±17,373
									Malig 27.3	Malig 1.2	Malig 7.8±6.6	Malig 16,371±20,382
Steele[35]	2007	Retrospective	D	95,627	96.7	69.2±12.5	EOC+++		22	1.4	7.6±5.1	34,178

[a] 102 robotic patients

[b] From our 2007 analysis of total hospital costs for robotic colectomy[36]

A ACS-NSQIP (2005–2006), *B* Premier Inc.'s Perspective Rx Comparative Database (2004–2006), *C* University Health System Consortium (2003–2006), *D* National Inpatient Samples (2003–2004), *RRSC* robotic right and sigmoid colectomy, *EOC* elective open colon resections for cancer, *EOC+* elective open right, left, and sigmoid colectomy, *EOC++* elective open sigmoid colectomy (data reported in benign vs malignant categories), *EOC+++* elective open right, left, and sigmoid colectomy for cancer

laparoscopically savvy general surgeons are so reluctant to embrace robotic colectomy when laparoscopically novice urologists so quickly took up the robotics banner.

Future Plans

As we have gained experience using this modality, we have evolved our technique and practices. Currently, we are critically evaluating our intracorporeal anastomosis for right colectomy in an attempt to simplify this portion of the procedure. We are currently adopting and refining a single position technique for sigmoid colectomy which may further cut down on operative time and the potential for complications. Also, at this time, we employ three different methods for splenic flexure mobilization. These include the lateral to medial, medial to lateral, and an approach initiated from the lesser sac. We plan to study the advantages, disadvantages, operative times, and possible indications for each technique. This will likely affect which technique is relied upon primarily during our laparoscopic and robotic sigmoidectomies in the future. Fast track surgery is also a topic of great interest currently, and it may be worthwhile to study the effects of a robotic procedure on postoperative recovery and length of stay. Finally, we have yet to approach a total colectomy with the robot. The main obstacle is robot position since repositioning the device is difficult and time consuming. Perhaps when the surgical cart is lighter or hangs from the ceiling, total colectomy will be more feasible.

Conclusion

We report updates to our technical procedures in robotic right and sigmoid colectomies. These results add to the current robotic literature and reaffirm that the use of robotics in colorectal surgery is a safe and effective option. We feel that resident training using the robot is an important component of modern surgical education and demonstrate that residents can evolve to the primary surgeon in robotic surgery. Finally, we make note of the fact that the vast majority of colon surgery performed is not done by a minimally invasive approach. Given that other specialties have made the progression from open procedures to robotic procedures, it seems feasible that this would be possible in colon surgery. This is attractive given the previously discussed advantages of robotic surgery and its increasing availability. We question the commonly accepted belief that robotic colectomy is more expensive than open. This will continue to be a topic of great interest. Further research is needed to specifically address these concerns.

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ORIGINAL ARTICLE

MTSS1 Overexpression Correlates with Poor Prognosis in Colorectal Cancer

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Abstract
Background The aims of this study were to investigate metastasis suppressor 1 (MTSS1) expression in benign and malignant colorectal tissues and to explore its significance in the prognosis of colorectal cancer (CRC) patients.
Methods MTSS1 expression was detected by immunohistochemistry in CRC, colorectal adenomatous polyp (precancerous lesion) and normal colorectal tissues. The relationship between MTSS1 expression in CRC tissues and clinicopathologic factors was analyzed with Mann–Whitney *U* test. MTSS1 protein expression was observed by Western blot in CRC tissues and adjacent nontumor colorectal tissues. Two factors between MTSS1 expression and CRC patient tumor node metastasis (TNM) stage were analyzed by Spearman rank correlation analysis. The Kaplan–Meier method and log-rank test were employed to compare the overall survival between MTSS1 negative/weak positive expression group and MTSS1 strong positive expression group.
Results MTSS1 expression rates were significantly higher in CRC tissues (99 out of 135, 73.30%) than that in normal colorectal tissues (one out of seven, 14.29%), nontumor colorectal tissues (six out of 32, 18.75%), and adenomatous polyp tissues (four out of 15, 26.67%; $P=0.003$, $P<0.001$, $P=0.001$, respectively). The upregulated MTSS1 expression in CRC tissues was significantly correlated to poor differentiation ($P=0.005$), tissue invasion ($P=0.018$), high preoperative CEA level ($P=0.022$), present lymph node metastasis ($P=0.003$), and high TNM stage ($P=0.002$). MTSS1 expression was positively correlated with clinical TNM stage, that suggested the more advanced clinical TNM stage corresponding to the higher expression level of MTSS1 ($r_s=0.327$, $P<0.05$). Western blotting demonstrated that MTSS1 expression was upregulated in 25 of 32 CRC tissues (75.0%) compared to corresponding adjacent nontumor colorectal tissues. The overall 5-year survival of MTSS1 strong positive expression CRC patients was significantly shorter than that of MTSS1 negative and weakly positive expression group. In multivariate analysis, MTSS1 expression maintained independent prognostic influence on overall survival ($P=0.004$).
Conclusion MTSS1 may be a good biomarker to be applied in the clinical setting to predict the prognosis of CRC patients with completely resected.

Keywords Colorectal cancer · MTSS1 · Immunohistochemistry · Western blot · Prognosis

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Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide. In recent years, with the improvement of people's living conditions, changing of diet, and living habits, the incidence of colorectal cancer increases year by year.[1] The incidence, development, invasion, and metastasis of CRC are a multi-step and multi-factor complex process. It is regulated by many genes and involves a variety of gene activation, inactivation, or regulated disorder. Recurrence and metastasis of CRC is the leading cause of death in CRC

patients. One hot study of CRC is molecular mechanism in the world all the time.

Metastasis suppressor 1 (MTSS1), also known as missing in metastasis gene (MIM), was originally identified by Lee et al. as a potential metastasis-suppressor gene that was present in non-metastatic bladder cancer cell lines, but was not expressed in a metastatic bladder cancer cell line. This gene, located on human chromosome 8q24.1, encodes a 5.3 kb mRNA and a polypeptide predicted to be an actin-binding protein of 356 amino acids with homology to the WASp (Wiskott–Aldrich Syndrome protein) family.[2] The amino acid sequence of MIM encodes a protein that contains multiple function motifs, including a coiled-coil domain, a lysine-rich domain (LRD), serine-rich domain (SRD), proline-rich domain (PRD), and a WASP homology domain-2 (WH2) domain at its C-terminus.[3] MIM also shares a certain homology with insulin receptor substrate p53 (IRSp53) in a region of 250 amino acids at the N-terminus.[4] Previous studies have reported the existence of multiple MIM splicing transcripts, including MIM-A (the prototype of MIM that encodes only 356 amino acids), MIM-B (which encodes a protein product of 759 amino acids) and MIM-C (which contains an alternative exon and predicts a protein of 734 amino acids). The three carboxy-terminal homology >50%, MIM-B is the longest and most abundant protein in the cell.[5]It is the representative of MIM protein,[6] and MTSS1 encodes a protein product with the same amino acid sequence as MIM-B.[7] People regard MTSS1 as a potential metastasis suppressor gene and carry out a series of studies. Researches in the breast, bladder, prostate benign and malignant tissues supports that MTSS1 is a tumor metastasis suppressor gene, but more and more researches find that MTSS1 plays other roles in tumor progression. Until now, there has not been research reporting its role in CRC. In this study, we sought to determine MIM-B expression in human CRC patient specimens and evaluate the clinicopathologic implications of MTSS1 expression in CRC, in an attempt to discover the potential influence of MTSS1 in the development of CRC.

Materials and Methods

Patient Specimens

A total of 135 patients with CRC received surgical treatment at Affiliated Hospital of Nantong University, from January 2004 to January 2005, and were enrolled in this study. Of them, 112 (83.0%) patients underwent potentially curative resection (according to the International Union Against Cancer (UICC) criteria). Twenty-four of 54 rectal cancer patients (44.4%) received TME surgical treatment. We categorized colon cancer patients into two groups by the number of lymph nodes recovered: (1) 0–11 lymph nodes, 17 examples (20.99%); (2) ≥12 lymph nodes, 64 examples (79.01%). Staging and grading were referred to the fifth edition of the tumor node metastasis (TNM) classification of UICC. Patients with stage I and stage II low-risk disease did not undergo fluorouracil-based adjuvant chemotherapy. If no contraindications were present, patients with stage II high-risk disease (pT4 and/or gross volume tumors, perforation, obstruction, poorly differentiated histology, long-lasting symptoms, elevated carcinoembryonic antigen (CEA) preoperatively, blood or lymphatic vessel invasion) and patients with stages III–IV underwent six cycles of fluorouracil-based adjuvant chemotherapy. Ninety-four patients (69.6%) underwent adjuvant chemotherapy. All patients were not to pass through preoperative radiotherapy or chemotherapy.

A total of 15 patients with colorectal adenomatous polyp received surgical treatment at our hospital were confirmed by postoperative pathology. Randomly selected adjacent non-tumor tissue specimens were obtained from 32 patients who underwent curative CRC surgery. They were taken more than 3 cm from the tumor margin and confirmed by pathology. Seven normal colorectal tissues were recruited from healthy living donors at our hospital. All donors were examined to be free of colorectal diseases. The histologic sections were reviewed by two expert pathologists (H.H. and ZH.J.) who had no knowledge of the patients' clinical status to verify the histologic diagnosis. The study was conducted with the approval of the institutional ethics board of our institute.

Methods

Immunohistochemistry

Tissues were de-waxed in xylene, rehydrated in alcohol, and immersed in 3% hydrogen peroxide for 5 min to suppress endogenous peroxidase activity. Antigen retrieval was performed by heating (100°C) each section for 30 min in 0.01 mol/L sodium citrate buffer (pH 6.0). After three rinses (each for 5 min in phosphate buffered saline (PBS)), sections were incubated for 1 h at room temperature with a polyclonal rabbit anti-human MTSS1 (ab78161) antibody (1:50; abcam, Cambridge, UK) diluted in PBS. After three washes (each for 5 min in PBS), sections were incubated with biotin-labeled secondary immunoglobulin for 1 h at room temperature. After three additional washes, peroxidase activity was developed with diaminobenzidine (DAB; DAKO, Glostrup, Denmark) at room temperature.

All slices were evaluated without knowledge of the clinical outcome. MTSS1 protein expression in benign and malignant colorectal tissues was evaluated by two individuals (M.R. and J.Z.) under an Olympus BX51 microscope (Olympus, Center Valley, PA). At least 200 tumor cells

were scored per ×40 field. All sections were scored in a semiquantitative manner according to the method described previously, which reflects both the intensity and percentage of cells staining at each intensity.[8] Intensity was classified as 0 (no staining), +1 (weak staining), +2 (distinct staining), or +3 (very strong staining). A value designated the "HSCORE" was obtained for each slide by using the following algorithm: HSCORE=$\sum(I\times PC)$, where I and PC represent staining intensity and the percentage of cells that stain at each intensity, respectively, and the corresponding HSCOREs were calculated separately. Sections were considered positive for MTSS1 when more than 25% of tumor cells were stained in the cell cytoplasm. Staining was scored independently by the two individuals who were blinded to each other's findings.

Western Blot Analyses

Thirty-two pairs of randomly selected nontumor and CRC patient tissue specimens were subjected to Western blot analysis. Total protein was extracted by radioimmunoprecipitation assay buffer. Equal amounts of protein separated by 10% sulfate polyacrylamide gel electrophoresis and then transferred to a polyvinylidene fluoride (PVDF) membrane. Nonspecific binding was blocked for 2 h with 5% nonfat milk in TBST (Tris-buffered saline containing 0.1% Tween-20). After incubation with the primary antibodies over night at 4°C (polyclonal rabbit anti-human MTSS1 at 1:200 dilution (Abcam, Cambridge, UK) or a rabbit anti- ß-actin as internal reference, at 1:1,000 dilution (Sigma-Aldrich, St. Louis, MO, USA)), membranes were washed three times in TBST for 5 min and subsequently incubated with a peroxidase-conjugated goat anti-rabbit secondary antibody (1:1,000 dilution, Sigma-Aldrich) for 2 h at room temperature, and developed using a chemiluminescence system (Pierce, Rockford, IL, USA). The film was visualized with enhanced chemiluminescence (Amersham Biosciences, Piscataway, NJ, USA).

Statistical Analysis

Correlations between clinicopathological factors and MTSS1 expression were analyzed by using Mann–Whitney U test. Two factors between MTSS1 expression and CRC patients TNM stage were analyzed by Spearman rank correlation analysis. Survival was calculated by the Kaplan–Meier method, and differences in survival were determined by the log-rank analysis. A multivariable analysis of several independent prognostic factors was carried out using Cox's proportional hazards regression model. Significance was defined as $P<0.05$. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc, Chicago, IL, USA).

Results

MTSS1 Expression in Benign and Malignant Colorectal Tissues

Immunostaining of MTSS1 in benign and malignant colorectal tissues was detected as brown–yellow granules in the cytoplasm (Fig. 1). Overall, MTSS1 expression was positive in 99 of 135 CRC tissues (73.33%), including 45 cases of strong expression (33.33%; Fig. 1a) and weak in 54 cases (40.00%; Fig. 1b). In the adenomatous polyp and normal colorectal tissues were mostly negative and a few weak positive MTSS1 expression in the cytoplasmic region (Fig. 1c and d).

Overall, one of seven colorectal normal tissues (14.29%) had positive MTSS1 expression, 6 of 32 colorectal nontumor tissues (18.75%) had positive MTSS1 expression, 4 of 15 colorectal adenomatous polyp tissues (26.67%) had positive MTSS1 expression, and the difference did not have statistically significant ($P>0.05$). Ninety-nine of 135 CRC tissues (73.33%) had positive MTSS1 expression and compared with colorectal normal tissues, colorectal nontumor tissues, and adenomatous polyp tissues, and the difference had statistically significant ($P<0.05$; Table 1).

MTSS1 Expression Is Correlated to Clinicopathologic Factors in CRC

Correlations between immunohistochemical MTSS1 expression in CRC tissues and various clinicopathologic characteristics of patients were analyzed by Mann–Whitney U test and listed in Table 2. Increased MTSS1 expression was found to be significantly related to poor differentiation ($P=0.005$), tissue invasion ($P=0.018$), high preoperative CEA level ($P=0.022$), present lymph node metastasis ($P=0.003$), and high TNM grade ($P=0.002$). Nevertheless, there was no significant correlation between MTSS1 expression and age, gender, tumor size, location, and preoperative CA19-9 level ($P>0.05$; Table 2).

Spearman rank correlation analysis was used to analyzed the relationship between MTSS1 expression in CRC and TNM stage, and it showed that MTSS expression in CRC was positive correlation with TNM stage, that suggested the more advanced clinical TNM stage corresponding to the higher expression level of MTSS1 in CRC ($r_s=0.327$, $P<40.001$; Table 3).

MTSS1 Protein Expression Is Upregulated in CRC

The protein expression of MTSS1 was examined by Western blot analysis in 32 randomly selected pairs of CRC and their matched nontumor colorectal tissues. MTSS1 protein was upregulated in the CRC samples

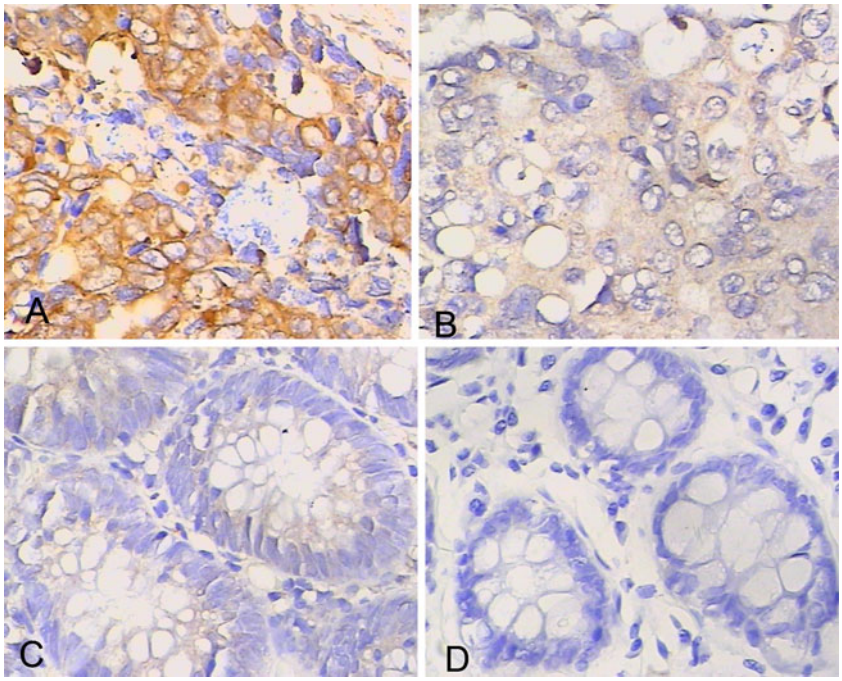

Fig. 1 Immunohistochemical staining of MTSS1 in benign and malignant colorectal tissues (×400). **a** strong positive expression in CRC tissues; **b** weakly positive expression in CRC tissues; **c** weakly positive in colorectal adenomatous polyp tissues; **d** negative expression in colorectal normal tissues

compared with their adjacent nontumor colorectal tissues in most of CRC patients (75%, 25 of 32 patients; Fig. 2).

MTSS1 Expression is Negatively Correlated to the Prognosis of CRC Patients

According to the immunohistochemical results of MTSS1 staining in tumor cells, CRC patients were divided into two groups including MTSS1 negative and weak positive (−~+) group and MTSS1 strong positive (++~+++) group. CRC patients underwent 5-years follow-up based on history, physical examination, complete blood count, liver function tests, ultrasound scan of the abdomen, and CEA monitoring every 3 months. Total body computed tomography scan and colonoscopy were done once a year. The overall survival was defined as the duration between the date of initial surgery and the date of death or the last follow-up for those still alive. In the process, seven patients lost to follow. The negative and weak positive (−~+) group had 86 cases, of which 34 cases died, and the 5-year overall survival rate was 60.5%. The strong positive (++~+++) group had 42 cases, of which 28 cases died, the 5-year overall survival rate was 33.3%. It was found that the overall survival of the negative and weak positive group was significantly longer than that of the strong positive group. For the purpose of seeing the true affect of MTSS1, we analyzed survival based on MTSS1 positivity by stage separating stage II and stage III from the rest of the group. The negative and weak positive (−~+) group had 56 cases, of which 18 cases died, and the 5-year overall survival rate was 67.9%. The strong positive (++~+++) group had 23 cases, of which 14 cases died, the 5-year overall survival rate was 39.1%. Likewise, the overall survival of the negative and weak positive group was significantly longer than that of the strong positive group. (a) CRC patients χ^2=10.631, P=0.001; (b)

Table 1 MTSS1 expression compared in benign and malignant colorectal tissues

Clinical parameters	Number	MTSS1 expression				Positive rate
		(−)	(+)	(++)	(+++)	
Normal tissue a	7	6	1	0	0	14.29%
Nontumor tissue b	32	26	6	0	0	18.75%
Adenomatous polyp c	15	11	3	1	0	26.67%
CRC d	135	36	54	34	11	73.33%

P value: *a*/*b*: p>0.05 (u value=107.000, p=0.783); *a*/*c*: p>0.05 (u value=45.000, p=0.499); *a*/*d*: p>0.05 (u value=171.000, p=0.003); *b*/*c*: p>0.05 (u value=218.000, p=0.480); *b*/*d*: p<0.05 (u value=846.000, p<0.001); *c*/*d*: p<0.05 (u value=494.000, p=0.001)

Table 2 The relationship between MTSS1 expression in CRC tissues and clinicopathological parameters

Clinical parameters	Number	MTSS1 expression				Positive rate	*P* value
		(−)	(+)	(++)	(+++)		
Sex							0.740
Male	71	19	30	16	6	73.2%	
Female	64	17	24	18	5	73.4%	
Age (years)							0.869
≥50	63	18	23	18	4	71.4%	
<50	72	18	31	16	7	75.0%	
Tumor size (cm)							0.324
≤5 cm	67	17	24	20	6	74.6%	
>5 cm	68	19	30	14	5	72.1%	
Location							0.643
Colon	81	23	32	19	7	70.4%	
Rectum	54	13	22	15	4	75.9%	
TNM stage							0.002
I+II	51	20	21	8	2	60.8%	
III+IV	84	16	33	26	9	81.0%	
Tissue invasion							0.018
T1/T2	74	24	31	16	3	67.6%	
T3/T4	61	12	23	18	8	80.3%	
Differentiation							0.005
Well/moderate	78	26	33	15	4	66.7%	
Poor	57	10	21	19	7	82.5%	
Preoperative CEA level							0.022
<4 ng/ml	47	19	16	9	3	59.6%	
≥4 ng/ml	88	17	38	25	8	80.7%	
Preoperative CA19-9 level							0.121
<60 U/ml	86	26	35	19	6	69.8%	
≥60 U/ml	49	10	19	15	5	79.6%	
Lymph node metastasis							0.003
None	79	27	33	14	5	65.8%	
Present	56	9	21	20	6	83.9%	

rectum cancer patients χ^2=4.958, P=0.026; (c) colon cancer patients χ^2=5.681, P=0.017; (d) stages II–III CRC patients χ^2=6.144, P=0.013; Fig. 3).

A multivariate analysis was performed to evaluate the independent prognostic roles of MTSS1 after adjusting for other significant covariates. All variables that significantly affected survival in univariate analysis were introduced into a Cox proportional-hazard model (Table 4). We can know that lymph node metastasis, TNM stage, differentiation, tumor invasion, and MTSS1 expression influenced overall survival in CRC patients (P=0.009, <0.001, 0.015, 0.019, and 0.004, respectively).

Table 3 Correlation analysis MTSS1 expression in CRC and TNM stage

TNM stage	MTSS1 expression				Total	r_s	*P* value
	(−)	(+)	(++)	(+++)			
I	10	6	1	1	18		
II	10	15	7	1	33		
III	11	22	12	4	49	0.327	<0.001
IV	5	11	14	5	35		
Total	36	54	34	11	135		

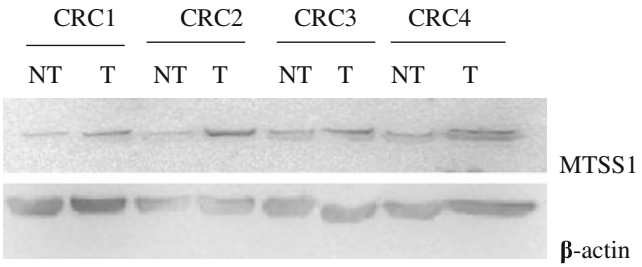

Fig. 2 Western blot analysis of MTSS1 proteins expressed in four pairs representative *CRC* tissues and their matched adjacent nontumor counterparts. β-actin was used as a control for equal loading. Abbreviations: *T* tumor tissues, *NT* nontumor tissues

Discussion

The original MIM variant was first described by Lee et al. as a potential metastasis suppressor in bladder cancer.[2] Wang et al. demonstrated that downregulation of MIM gene is associated with the progression of bladder transitional carcinomas.[6] Down-regulation of MIM expression can occur in bladder cancer cell lines but is not associated with increased invasive behavior and is unlikely to be due to promoter hypermethylation or loss of p53 function.[9] Expression of MIM has also been shown to be reduced in prostate cancer; but contrary to results obtained in bladder cancer, reduction in MIM gene expression in the prostate can contribute to tumor growth and development, as well as metastasis.[5] Parr and Jiang [10] reported that breast cancer patients expressing reduced levels of MTSS1 had a poorer prognosis. High levels of MTSS1 were correlated with an increased patient overall survival and disease-free survival. Liu et al.[11] demonstrated that downregulation of MTSS1 is associated with nodal metastasis and poor outcome in Chinese patients with gastric cancer.

But there is accumulating evidence showing that MTSS1 is unlikely a metastasis suppressor. Likewise, our study does not support that MTSS1 is a metastasis suppressor. Because MTSS1 expression in CRC was significantly higher than other colorectal tissues. MTSS1 expression was positively correlated with TNM staging and lymphatic invasion status in CRC. The overall 5-year survival of MTSS1 strong positive expression group was significantly shorter than that of MTSS1 negative and weakly positive expression group. Callahan et al.[12] found that MTSS1 is up-regulated in basal cell carcinomas. And it is a member of the sonic hedgehog signaling pathway that modulates Gli responses during growth and carcinogenesis. MIM-B induced actin-rich protrusions resembling microspikes and lamellipodia at the plasma membrane and promoted disassembly of actin stress fibers MIM-B possibly is downstream of tyrosine kinase signaling.[13] MIM seems to play a role in cytoskeleton remodeling.[4] Linet al.[3] demonstrated that MIM activates markedly cortactin but attenuates N-WASp-mediated actin polymerization. MIM may be implicated in cell motility by modulating different actin polymerization factors. Utikal et al.[14] reported that an

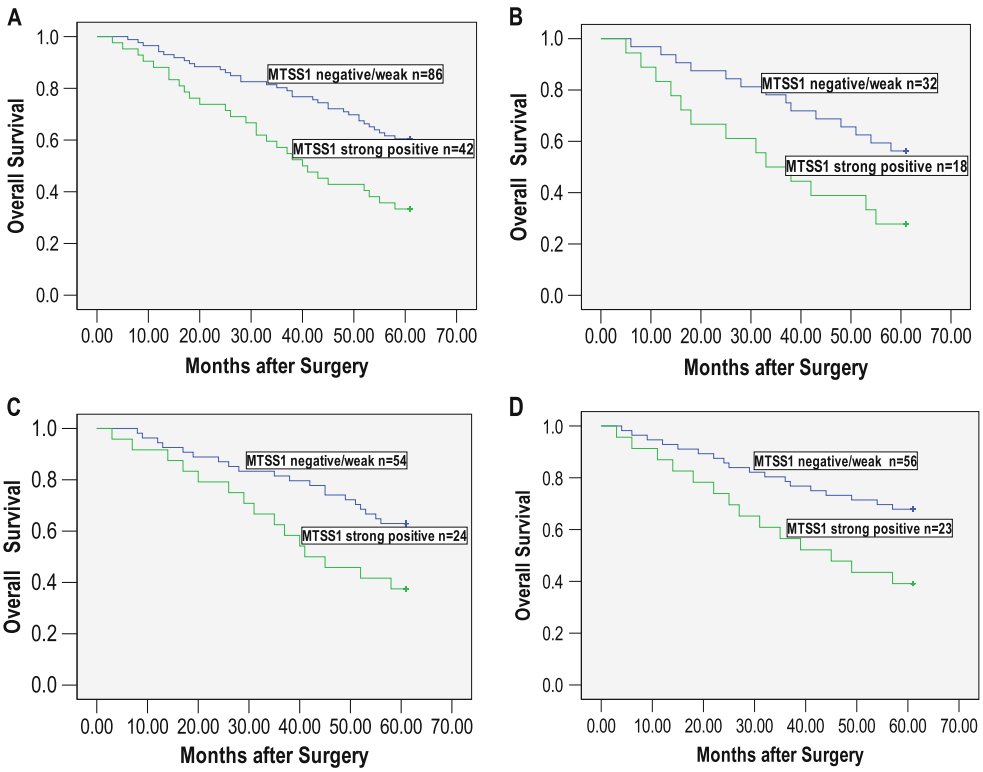

Fig. 3 Comparison of different overall survival cumulative Kaplan–Meier curves for patients grouped by immunohistochemical levels of MTSS1. **a** CRC patients. **b** Rectum cancer patients. **c** Colon cancer patients. **d** Stages II–III CRC patients

Table 4 Cox proportional hazards model analysis of prognostic factors

Factors	Characteristics		Hazard ratio	95% CI	*P* value
	Unfavorable	Favorable			
Lymph node metastasis	Present	None	1.601	1.225–2.572	0.009
TNM stage	III/IV	I/II	2.792	1.473–3.650	<0.001
Adjuvant chemotherapy	No	Yes	1.372	0.896–2.078	0.474
Differentiation	Poor	Well/moderate	1.521	1.275–2.091	0.015
Preoperative CEA level	≥4 ng/ml	<4 ng/ml	1.178	0.641–2.114	0.623
Tumor invasion	pT3/pT4	pT1/pT2	1.587	1.201–2.210	0.019
MTSS1 expression	Positive	Negative/weak	2.451	1.348–2.899	0.004

increase in DNA methylation density in the promoter for MIM correlated with the silencing of MIM expression and found that inhibiting DNA methylation using 5-Aza-dC led to an increase in expression. Huang et al.[15] found that MTSSI encoded a protein of MIM-B was situated in the central position of gene function net of residual HCC. Ma et al.[16] found that MIM-B mRNA and protein is overexpressed in hepatocellular carcinoma. Higher levels of MIM-B expression were found to be associated with early stage disease. Endogenous MIM is induced by hedgehog signaling and localizes to actin bundles. MIM induces cytoskeletal changes independently of the WH2 domain through actin bundling. MIM binds to RPTPδ and relocalizes it to the membrane. MIM cooperates with RPTP to induce cytoskeletal changes.[17] MIM knockdown results in increased Src kinase activity and subsequent hyperphosphorylation of the actin regulator cortactin. MIM-dependent inhibition of Src and cortactin is required MIM and cortactin antagonism regulates ciliogenesis and hedgehog signaling.[18]

Given that CRC is one of the most malignant cancers in the world and that tumor recurrence and metastases are the major causes of death in patients with CRC, resulting in a poor prognosis of the disease, we set out to examine the role of MTSS1 in CRC. The study found that MTSS1 expression in CRC was significantly higher than normal colorectal tissues, nontumor colorectal tissues, and adenomatous polyp tissues (P=0.003, P<0.001, P=0.001, respectively). The overall 5-year survival of MTSS1 strong positive expression group was significantly shorter than that of MTSS1 negative and weakly positive expression group. The survival analyses performed separately for colon cancer or rectal cancer, and stratified according to MTSS1 expression, showed that MTSS1 expression was a significant prognostic factor for overall survival in patients with colon cancer or rectal cancer. For the purpose of seeing the true affect of MTSS1, we analyzed survival based on MTSS1 positivity by stage separating stage II and stage III from the rest of the group. The overall 5-year survival of MTSS1 strong positive expression group was also significantly shorter than that of MTSS1 negative and weakly positive expression group (χ^2=6.144, P=0.013). MTSS1 expression was found to be significantly correlated with prognosis in univariate survival analysis and it still kept its prognostic value in multivariate survival analysis. It indicates that MTSS1 high expression may predict poor prognosis. Because MTSS1 has not been clearly defined to date because of contradicting published data, we speculate that the role of MTSS1 could be cancer or tissue type specific or play other roles in the development of tumor invasion and metastasis. Overexpression of MTSS1 was correlated with poor differentiation, tissue invasion, high preoperative CEA level, present lymph node metastasis, and high TNM grade (P=0.005, 0.018, 0.022, 0.003 and 0.002, respectively). It suggests that MTSS1 plays an important role in CRC invasion, progression, and metastasis. MTSS1 involved in CRC and other tumors precise mechanism is not clear. Further functional investigations are worthwhile to explore the precise mechanism of the carcinogenic effect of MTSS1, meanwhile, provide a new research field and target for diagnosing and treating CRC and other tumors.

Conclusion

To the best of our knowledge, this is the first report that demonstrates the involvement of MTSS1 in the carcinogenesis of CRC. In this study, we found a significant increase in MTSS1 expression from normal colorectal tissues and colorectal adenomatous polyp to CRC. In CRC patients, overexpression of MTSS1 was correlated with poor differentiation, tissue invasion, high preoperative CEA level, present lymph node metastasis, and high TNM grade. The overall survival of MTSS1 strong positive expression CRC group was significantly shorter than that of MTSS1 negative and weakly positive expression CRC group. MTSS1 expression may serve as a useful biomarker for the prediction of outcome of CRC.

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ORIGINAL ARTICLE

Clinicopathologic Characteristics and Outcomes of Patients with Obstructive Colorectal Cancer

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Abstract
Purpose The aim of this retrospective study was to analyze the clinicopathologic characteristics and short-term and long-term outcomes of colorectal cancer patients with obstruction compared to those of non-obstructive colorectal cancer patients.
Methods Between January 1998 and December 2005, 1,672 colorectal cancer patients undergoing operation were enrolled in this study. Patients were classified into two groups according to the presentation: patients with complete obstructive colorectal cancer (COC, n=215) receiving emergency procedures and patients with non-obstructive colorectal cancer (NOC, n=1,457) receiving elective procedures. The data on the clinicopathologic characteristics and short-term and long-term outcomes of patients were analyzed retrospectively.
Results Among 1,672 colorectal cancer patients, 215 cases presented with complete obstruction. The distribution of tumor location and size, macroscopic type, depth of invasion, liver metastasis, peritoneal carcinomatosis, and TNM stage were found to be different between the COC and NOC groups. Logistic regression analysis showed that tumor location, depth of invasion, and peritoneal carcinomatosis were independent factors associated with obstruction. Patients with obstruction had an increased risk of death by a factor of 2.251 compared to patients without obstruction. Peritoneal carcinomatosis and TNM stage were independent factors for the survival of the COC group. Obstruction, peritoneal carcinomatosis, tumor macroscopic type, and TNM stage were independent indicators for postoperative recurrence. Postoperative mortality was significantly higher in the COC group than the NOC group. The overall 5- and 10-year survival rates in the COC group were 47.8% and 42.8%, respectively, compared to 67.2% and 59.8% in the NOC group, respectively (p<0.05). The postoperative recurrence rates were 43.1% in the COC group and 32.8% in the NOC group (p<0.05).
Conclusions Obstruction is an independent indicator for the survival and postoperative recurrence for patients with colorectal cancer. Patients in the COC group have worse overall survival with high postoperative recurrence rate compared to those in the NOC group.

Keywords Colorectal cancer · Obstruction · Prognosis · Recurrence

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Introduction

Colorectal cancer (CRC) is the third and fourth most common cancer in urban and rural districts in China,

respectively, which is difficult to diagnose due to early atypical symptoms and signs. A large number of patients with CRC are not identified until the advanced stage or upon presentation with intestinal obstruction or other emergency situations. The incidence of obstruction has been reported to be about 7% to 47% of among CRC patients and accounts for about 85% of colonic emergencies.[1–5]

It has been reported that CRC patients with obstruction have an advanced stage and worse long-term survival compared to non-obstructive CRC, with a 5-year survival rate ranging from 12% to 31%[6–12] and a higher proportion of liver metastasis.[13] Other differences are also significant between the two groups in clinicopathologic characteristics, postoperative morbidity and mortality, recurrence, and so on. Although the impact of obstruction on postoperative outcomes has been well documented, few data were available for CRC patients with obstruction in China mainland. Therefore, in the present study, clinicopathologic characteristics and short-term and long-term outcomes of patients with obstructing CRC were retrospectively assessed compared to those of patients with non-obstructing CRC.

Patients and Methods

Between January 1998 and December 2005, 1,672 CRC patients were diagnosed and treated with surgery at our hospital, and all tumors were histologically determined to be adenocarcinoma. Patients were divided into two groups according to the presentation: patients with completely obstructive colorectal cancer (COC, n=215) who received emergency procedures and patients with non-obstructive colorectal cancer (NOC, n=1,457) who received elective procedures. Complete bowel obstruction was diagnosed by medical history, physical examination, abdominal computed tomography (CT) scan and colonoscopy features, and surgical findings. Emergency surgical operation was performed within 24 h after diagnosis. No CRC patients with obstruction received stent placement in this study during the period of 1998–2005. Postoperative mortality was defined as death occurring within 30 days after the main surgical operation. Overall survival rate at 5 and 10 years were considered the crude survival rate and included all causes of death. Patients who died within 30 days after operation were excluded in the analysis of survival. The patients at TNM stage II with high risk

Table 1 Demographic and patients characteristics of colorectal cancers with or without obstruction

Indicator	Obstruction		χ^2	p value
	No	Yes		
Age (years)	57.8±13.9 (18–91)	59.3±15.4 (17–99)		0.140
Gender			0.532	0.407
Male	829	128		
Female	628	87		
Age group			1.440	0.487
≤40	191	27		
41–64	731	100		
≥65	535	88		
Hospital stay (days)	14.3±8.4	17.5±9.1		0.216
Site of CRC			45.333	<0.0001
Colon	646	148		
Rectum	813	67		
Site of colon cancer			13.538	<0.0001
Right-sided	357	57		
Left-sided	289	91		
ASA score			0.055	0.815
I/II	1,142	157		
III/IV	315	48		
Surgical procedure			23.499	<0.0001
Curative	1,333	174		
Palliative	99	33		
Others[a]	25	8		
Chemotherapy			0.147	0.701
No	442	68		
Yes	1,015	147		

[a] Colostomy, bypass, or indeterminate procedures

factors and TNM stages III–VI were treated with adjuvant chemotherapy within 1 month after operation. 5-Fu/CF regimes as first-line treatment were administered during 1995–2000, and FOLFOX regimes were administered during 2001–2005.

Clinicopathologic factors of CRC patients were encoded to form a computerized database. The recorded variables included: (1) age, gender, family history, and comorbidity of the patient, (2) location, size, macroscopic type, differentiation, and TNM stage of tumor, and (3) types of operation, postoperative complications, recurrence, and status at last follow-up end point. All the patients were followed up with physical examination, hematological–biochemical examinations, serum carcinoembryonic antigen level assay, chest X-ray, and abdominal and/or pelvic CT scan every 3 months during the first 1 year, every 6 months during the subsequent 2 years, and then once a year. Follow-up was made by clinic appointments, home visits, or letters/phone calls to update information constantly. The follow-up end point was December 2009.

The colon was divided into the left- and right-sided segments, and the junction was defined as the distal third of the transverse colon. Operative procedure was specified as curative, palliative, or bypass/colostomy. Curative procedure was considered a complete resection of the cancer and no residual malignancy, local or distant, was present. Palliative procedure was considered if residual malignancy was present locally or at a distant site after an operation.

Statistical analysis was performed using the program SPSS for Windows Version10.0 (SPSS, Chicago, IL, USA). Numerical data were compared by *t* test and nominal data by chi-square test or Fisher's exact test. The variables considered were age, gender, location and size of tumor, pathologic features, curative resection rate, and postoperative outcomes. Significant variables at univariate analysis were included into a multivariate stepwise Cox proportional hazard regression model analysis to identify independent factors related with obstructive CRC and survival. The overall survival was calculated with the Kaplan–Meier method, and the differences in survival were compared by log-rank test. The differences between the two groups were considered statistically significant if the p value was ≤ 0.05.

This study was approved by the Ethics Committee of Sun Yat-sen University and consistent with the tenets of the Declaration of Helsinki for biomedical research involving human subjects. All patients included in the study gave their informed consent.

Results

Patients and Tumor Characteristics

A total of 1,672 patients with known modes of presentation underwent surgery for CRC between 1998 and 2005; of which, 215 cases were completely obstructive cases that received emergency surgery and represented 13% of the total CRC patients. There were 1,457 elective patients (87%). In the present study, the follow-up time ranged from 6 to 12 years with a median time of 10 years.

The demographic, patient's characteristics, and pathologic characteristics of colorectal cancer were summarized in Tables 1 and 2. The mean age was 59.3±15.4 years in

Table 2 Pathologic characteristics of colorectal cancers with or without obstruction

Indicator	Obstruction		χ^2	p value
	No	Yes		
Tumor size(cm)			6.461	0.011
≤5	1,038	133		
>5	419	82		
Macroscopic type			30.111	<0.0001
Polyploid	595	84		
Ulcerative	685	76		
Infiltrative	177	55		
Depth of invasion			42.278	<0.0001
T1	67	6		
T2	343	11		
T3	912	169		
T4	135	29		
Nodes involvement			0.027	0.868
No	392	59		
Yes	1,065	156	0.328	0.567
N1	380	52		
N2	685	104		
Liver metastasis			10.616	0.001
No	1,354	186		
Yes	103	29		
Histological grade			1.851	0.396
Well differentiated	532	82		
Moderately differentiated	772	105		
Poorly differentiated	153	28		
TNM stage			31.244	<0.0001
I	175	6		
II	617	92		
III	454	61		
IV	211	56		
Histological type			4.197	0.123
Adenocarcinoma	1,302	182		
Mucinous adenocarcinoma	125	27		
Signet ring cell tumor	30	6		
Peritoneal carcinomatosis			25.895	<0.0001
No	1,368	181		
Yes	89	34		
Disease recurrence			11.361	0.001
No	896	99		
Yes	437	75		

Table 3 Binary logistic regression analysis of pathologic factors associated with obstruction

	β	χ^2	p value	95% CI
Tumor location	−0.951	31.130	<0.0001	0.378 (0.277–0.540)
Tumor size	0.109	0.394	0.530	1.115 (0.794–1.565)
Depth of invasion	0.449	9.124	0.003	1.567 (1.171–2.097)
Macroscopic type	0.122	2.026	0.155	1.129 (0.955–1.336)
Liver metastasis	0.525	3.533	0.060	1.690 (0.978–2.921)
TNM stage	0.099	0.726	0.394	1.104 (0.880–1.385)
Peritoneal carcinomatosis	0.654	6.516	0.011	1.924 (1.164–3.179)

CI confidence interval

the COC group and 57.8±13.9 years in the NOC group (p=0.140). Chemotherapy regimes were similar and no statistical difference was found in the percentage of patients receiving chemotherapy (p=0.701) between the two groups. The groups were also compared for gender, ASA score, nodes involvement, histopathologic differentiation and types, and hospital stay (p=NS).

The distribution of tumor location was significantly different between the two groups. Of 215 cases with obstruction, 67 had tumor at the rectum, 57 at the right-sided colon, and 91 at the left-sided colon. More colon cancers with obstruction were found in the COC group than in the NOC group (68.8% vs. 44.3%, p<0.0001). Further analysis showed that left-sided colon cancer was more common than right-sided colon cancer in the COC group compared to the NOC group (61.5% vs. 44.7%, p<0.0001).

There was a significantly higher proportion of advanced TNM stage III/IV cancer in the COC group than in the NOC group (54.4% vs. 45.6%, p=0.016). The significant differences by univariate analysis were also found in surgical procedure (p<0.0001), tumor size (p=0.011), tumor macroscopic type (p<0.0001), depth of invasion (p<0.0001), liver metastasis (p=0.001), peritoneal carcinomatosis (p<0.0001), TNM stage (p<0.0001), and disease recurrence (p=0.001) between the two groups (Tables 1 and 2). Based on binary logistic regression analysis, pathologic factors such as tumor location, depth of invasion, and peritoneal carcinomatosis were independently associated with obstruction after adjusting for differences in tumor size, TNM stage, tumor macroscopic type, and liver metastasis (Table 3). When obstructing CRC patients were divided into two groups by location, colon cancer and rectal cancer groups, no significant difference was found between them in demographic and clinicopathologic features.

Several concomitant diseases were found in 109 patients in the COC group and 585 patients in the NOC group (51.2% vs. 40.4%, p=0.002). Chronic pulmonary diseases, cardiovascular disorders, hypertension, insulin-dependent diabetes, and renal dysfunction were common concomitant diseases.

Short-Term Outcomes

The average length of hospitalization in the cohort was 15±4.3 days with a range from 12 to 45 days. The mean hospital stay in the COC group (14.3±8.4 days) and in the NOC group (17.5±9.1 days) was not significantly different (p=0.216). The overall curative resection rate was 89.2% for the two groups. A relatively lower curative resection rate was found in the COC group than in the NOC group (82.2% vs. 92.3%, p<0.0001).

The overall postoperative mortality within 30 days of surgery was 5.1% (n=85) for all patients, and the postoperative mortality was high in the COC group compared to the NOC group (7.9%, n=17 vs. 4.7%, n=68; p=0.044). Eleven cases with colon cancer and 6 cases with rectal cancer died within 30 days after operation in the COC group, while 42 cases with colon cancer and 26 cases with rectal cancer died in the NOC group.

The survivors and the non-survivors in the COC group were compared regarding demographic and clinicopathologic characteristics, concomitant diseases, and compli-

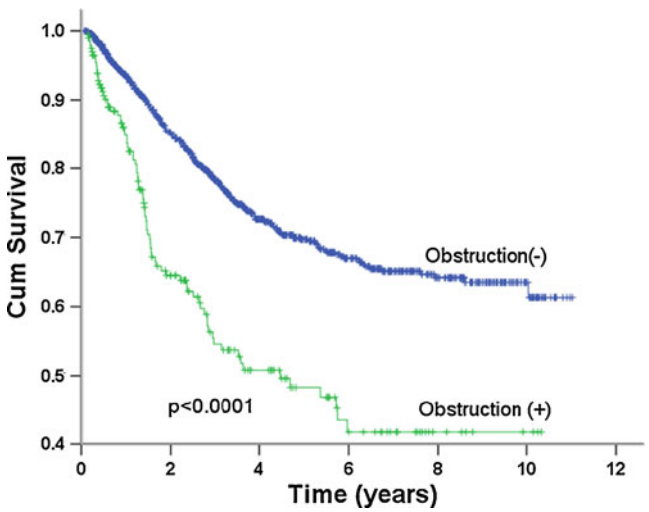

Fig. 1 Cumulative survival probability according to the presence or absence of obstruction at presentation, p<0.0001

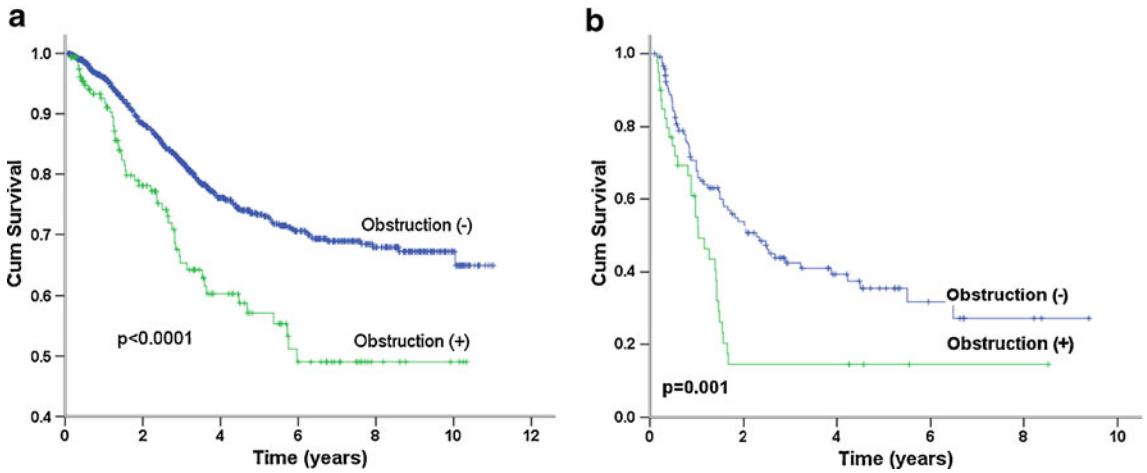

Fig. 2 Cumulative survival probability according to obstruction by procedure. **a** Comparison in patients undergoing radical resection between the two groups, $p<0.0001$; **b** comparison in patients undergoing incurable resection between the two groups, $p=0.001$

cations, and the results were as follows: mean age, 47.1± 12.3 vs. 63.4±14.2 years, $p=0.018$; ASA score III/IV, 18.2% ($n=36$) vs. 70.6% ($n=12$), $p=0.003$; infiltrative tumor, 23.7% ($n=47$) vs. 47.1% ($n=8$), $p=0.034$; concomitant diseases, 47.5% ($n=94$) vs. 88.2% ($n=15$), $p=0.001$; and complications, 32.3% ($n=64$) vs. 76.5% ($n=13$), $p<0.0001$. No significant difference was found in other pathologic factors between survivors and non-survivors. Mortality was independently related to concomitant diseases ($p<0.0001$), obstruction ($p=0.001$), and complication ($p<0.0001$). The postoperative complications in the COC group (35.8%, $n=77$) and in the NOC group (40.6%, $n=591$) were not significantly different ($p=0.184$).

Long-Term Outcomes

The overall 5- and 10-year survival rates of all CRC patients were 64% and 57%, respectively, with a median survival time of 11 years. The overall 5- and 10-year survival rates were 43% and 36% in the COC group, respectively, compared to 67% and 60% in the NOC group, respectively. The median survival time was 4.6 years in the COC group and 11 years in the NOC group. Comparison of survival curves between the COC and the NOC groups was presented in Fig. 1. Obstructive CRC patients receiving emergency procedures did have significantly worse overall 5-year survival than non-obstructive CRC patients receiving elective procedures (43% vs. 67%, $p<0.0001$).

With respect to patients who underwent curative resection, the overall 5- and 10-year survival rates were 57% and 48% in the COC group, respectively, and 71% and 63% in the NOC group, respectively ($p<0.0001$; Fig. 2a). Similar results were found in the overall 5- and 10-year survival rates of patients who underwent non-curative resection ($p=0.001$; Fig. 2b). On stage-for-stage analysis for survival, the overall 5- and 10-year survival rates were 92% and 74%, respectively, in the COC group and 95% and 80%, respectively, in the NOC group for patients at TNM stage I; 60% and 60%, respectively, in the COC group and 79% and 76%, respectively, in the NOC group at TNM stage II; 38% and 38%, respectively, in the COC group and 62% and 60%, respectively, in the NOC group at TNM stage III; and 18% and 0%, respectively, in the COC group and 19% and 0%, respectively, in the NOC group at TNM stage IV (Table 4). Compared to the NOC group, the COC group had a worse 5-year overall survival rate for TNM stage II patients (79% vs. 60%, $p=0.001$) or stage III patients (62% vs. 38%, $p<0.0001$), but not for the TNM stage I patients (95% vs. 92%, $p=0.266$) or stage IV patients (19% vs. 18%, $p=0.077$). When patients were divided into two

Table 4 Stage-specific overall survival of CRC patients by presentation

TNM stage	Obstruction	5-year OS (%)	10-year OS (%)	*p* value
I	No	95	80	0.266
	Yes	92	74	
II	No	79	76	0.001
	Yes	60	60	
III	No	62	60	<0.0001
	Yes	38	38	
IV	No	19	0	0.077
	Yes	18	0	

OS overall survival

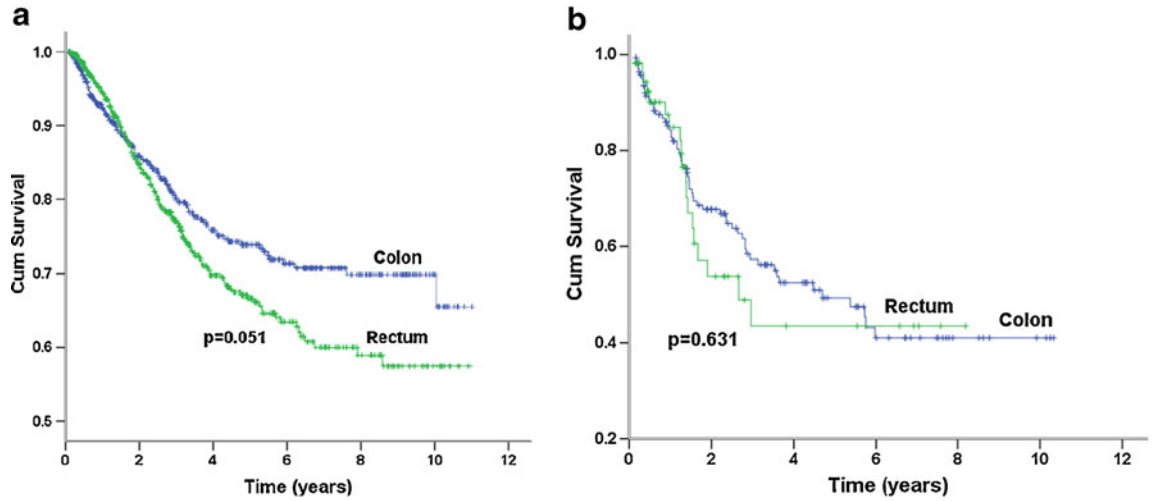

Fig. 3 Cumulative survival probability according to obstruction by tumor location. Both in the COC group and in the NOC group, no significant difference was found in the overall 5-year survival rate between the colon cancer group and rectal cancer group (**a** NOC group, $p=0.051$; **b** COC group, $p=0.631$)

groups by location, no significant difference was found in the overall 5-year survival rate between the colon cancer group and rectal cancer group both in the COC group and in the NOC group (Fig. 3).

Univariate and multivariate analyses demonstrated that obstruction was an independent predictor for the survival of CRC patients. Patients with obstructive CRC had an increased risk of death by a factor of 2.251 compared to non-obstructive CRC patients (Table 5). With regard to demographic and pathologic factors affecting the survival of obstructive CRC patients, univariate analysis showed that survival was significantly affected by nodes involvement ($p=0.039$), liver metastasis ($p<0.0001$), peritoneal carcinomatosis ($p<0.0001$), and TNM stage ($p<0.0001$), while other factors including gender, age, ASA score, histological grade and histological type, tumor location and size, tumor macroscopic type, and depth of invasion did not affect survival. In addition, multivariate analysis demonstrated that peritoneal carcinomatosis and TNM stage were independent factors for the survival of obstructive CRC patients (Table 6).

In the present study, the overall recurrence rate was 34% (512 out of 1,507) for CRC patients who underwent curative resection. Median intervals from radical surgery to recurrence were 18.3±5.4 months in the COC group and 21.5±8.1 months in the NOC group ($p=0.501$). During follow-up, 75 patients in the COC group and 437 patients in the NOC group were diagnosed as local and/or distant recurrence ($p=0.001$). In the COC group, 51 local and 17 distant recurrences were recorded, while in the NOC group, 260 local and 133 distant recurrences were recorded. In addition, 7 patients in the COC group and 44 patients in the NOC group were diagnosed as local associated with distant recurrence. Univariate analysis demonstrated that postoperative recurrence was associated with obstruction ($p<0.0001$), peritoneal carcinomatosis ($p<0.0001$), tumor macroscopic type ($p=0.001$), depth of invasion ($p<0.0001$), and TNM stage ($p<0.0001$). However, multivariate analysis showed that obstruction, tumor macroscopic type, and TNM stage were independent indicators for postoperative recurrence (Table 7).

Discussion

The survival of obstructive CRC patients is poor even in those undergoing potentially curative surgery. Moreover, the poor outcomes for obstructive CRC patients persist from initial hospital stay to long-term follow-up.[1–5]

In the present study, the incidence of complete obstruction in CRC patients was 13%, similar to the results in a previous report.[6] Moreover, the percentages of obstructive

Table 5 Five-year overall survival by presentation for CRC patients

Obstruction	No. of patients	Overall survival			χ^2	*p* value
		5-year OS (%)	HR	95% CI		
No	1,457	67	1	Reference	42.22	<0.0001
Yes	215	43	2.251	1.762–2.875		

OS overall survival, *CI* confidence interval, *HR* hazard ratio

Table 6 Univariate and multivariate analysis of the prognostic factors for 5-year overall survival of 215 CRC patients with obstruction

Indicator	Univariate analysis		Multivariate analysis		
	5-year OS (%)	*p* value	HR	95% CI	*p* value
Gender		0.550			NS
Male	41				
Female	45				
Age group (years)		0.07			NS
≤40	38				
41–64	56				
≥65	34				
Location of CRC		0.631			NS
Colon	42				
Rectum	47				
Blood transfusion		0.299			NS
No	52				
Yes	40				
Family history		0.8			NS
No	43				
Yes	47				
Tumor size(cm)		0.238			NS
≤5	45				
>5	43				
Macroscopic type		0.868			NS
Polyploid	46				
Ulcerative	43				
Infiltrative	37				
Nodes involvement		0.039			0.062
No	49		1	Reference	
Yes	38		1.444	0.193–10.823	
Depth of invasion		0.403			NS
T1	75				
T2	54				
T3	44				
T4	33				
Liver metastasis		0.000			0.192
No	47		1	Reference	
Yes	15		1.551	0.802–2.997	
Histological grade		0.514			NS
Well differentiated	49				
Moderately differentiated	43				
Poorly differentiated	39				
Peritoneal carcinomatosis		0.000			0.032
No	46		1		
Yes	25		1.828	1.052–3.175	
TNM stage		0.000			0.001
I	100		1	Reference	
II	60		1.387	0.185–10.393	
III	38		3.396	0.459–25.142	
IV	18		4.793	0.622–36.918	
Histological type		0.901			NS
Adenocarcinoma	58				
Mucinous	43				
Signet ring					

OS overall survival, *CI* confidence interval, *HR* hazard ratio

Table 7 Multivariate analysis of postoperative recurrence

Variable	HR	95% CI	*p* value
Obstruction	1.502	1.147–2.126	0.032
Macroscopic type	1.724	1.557–2.174	0.008
TNM stage	2.80	2.593–3.048	<0.0001

CI confidence interval

CRC patients and advanced cancer in different age groups were not statistically different, although previous studies suggest that patients aged <40 or >80 years were more likely to have large bowel obstruction and advanced Duke-staged cancer.[7–10] Malignant obstruction can occur at any part of the colon and rectum; however, the risk varies with different locations. In this study, 42.3% of the obstructions occurred at the left-sided colon and most of them occurred at the sigmoid colon; this tumor distribution is similar to what has been reported by other investigators.[11–13] Although recent studies demonstrate similar radical resection rates for CRC patients receiving emergency and elective surgery,[14] the curative resection rate was significantly higher in the NOC group than in the COC group in the present study.

Emergency surgery for obstructive CRC has been documented to carry high rates of mortality and morbidity.[15,16] In terms of postoperative mortality, the overall postoperative mortality in the present study was 5.1%, including those patients with advanced unresectable tumors. Concomitant diseases and obstructions were so strongly associated with postoperative mortality that the mortality rate in the COC group is significantly higher than that in the NOC group. The result obtained from the study is consistent with other reports.[17,18] Although ASA score was associated with obstruction,[19] no significant difference was found between the COC and NOC groups. In terms of postoperative morbidity, the complications in the immediate postoperative period in the COC group (35.8%) and in the NOC group (40.6%) were not significantly different.

Although some reports have demonstrated that even T1 carcinoma may be the cause of obstruction, many studies show that obstructing colorectal cancers are either locally advanced or associated with distant metastasis. In the present study, the distribution of TNM stage III/IV was more common than TNM stage I/II in the COC group (15% vs. 11%, $p=0.026$). Previous studies revealed that the survival of CRC patients with obstruction is significantly related to tumor stage, histological type, and clinical and operative variables and that obstruction is not a significant indicator for survival.[20,21] However, in the present study, we found that obstruction is associated with survival based on both univariate analysis and multivariate Cox regression model. Patients with obstructive CRC had an increased risk of death by a factor of 2.251 compared to non-obstructive CRC patients.

Long-term prognosis of obstructive CRC patients undergoing emergency procedure has been reported to be worse compared to that of non-obstructive CRC patients receiving elective surgery.[22] Although a recent study reported that the negative effect of obstruction on colorectal cancer may be limited to the perioperative period and that long-term survival would depend on the tumor stage not on the presentation,[23] in the present study, apart from mortality, the overall 5- and 10-year survival rates were still worse in the COC group than in the NOC group. When patients were stratified according to tumor stage and stage-for-stage analysis on survival was performed, significant difference was found at TNM stage II or III, but not at TNM stage I or IV between the COC and the NOC group, which is different from previous studies.[14,24]

In our study, the overall recurrence rate was 34% consisting of 20.6% local recurrence, 10.0% distant recurrence alone, and 3.4% local and distant recurrences in the same patient. Local recurrence rate is significantly higher in the COC group than in the NOC group (29.3% vs. 17.3%, $p<0.0001$); however, no statistical difference was found in metastasis between the groups (10.8% vs. 8.8%, $p=0.679$). Our results show that obstruction is an independent indicator for postoperative recurrence, although some reports suggest that obstruction is not associated with local recurrence.[14,25] We postulate that the extent of tumor excision and lymph node dissection would have been limited because of the dilated bowel filled with a large amount of fecal material, edematous conditions of the bowel, and manipulation of the surgeons, which facilitated the spreading of the tumor cells into the lymphatic vessels, vasculature, and peritoneal cavity to cause recurrence. Therefore, for CRC patients with obstruction, one important measure is to decompress the dilated bowel by surgical procedure or non-surgical measures; on the other hand, much more attention should be paid to the patient with obstructing CRC receiving curative resection in order to detect early local and/or distant recurrence in future practice.

Compared to CRC patients undergoing elective surgery, patients undergoing emergency surgery have high morbidity and mortality rates, which was confirmed again in our study. Stent placement is a mini-invasive alternative to decompress an obstructed colon, which is widely used for the treatment of obstructing CRC. For patients with potentially curable obstructing CRC, stent insertion offers immediate and effective colon decompression and acts as a bridge to elective oncologic resection, which transfers about 90% obstructive CRC patients from emergency surgery to elective surgery with lower mortality and shorter hospital stay.[26–28] Even for patients with incurable obstruc-

tive CRC, stent insertion also provides the opportunity of chemotherapy to improve oncological outcomes.

As most retrospective studies, there were several limitations in the present study. First, the relatively small number of patients in our study may overlook some important factors which may predict the postoperative outcomes. Second, such pathologic factors as lymphovascular and perineural invasion were not investigated in this study. In addition, patients who were managed by non-operative options, such as the using of stents as a bridge to surgery, were not included in this study.

Conclusion

CRC patients with obstruction have significant differences in clinicopathologic features compared to those CRC patients without obstruction. Obstruction is an independent indicator for survival and postoperative recurrence for patients with colorectal cancer. Patients in the COC group have worse survival with higher postoperative recurrence rate compared to those in the NOC group.

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Conflict of Interest The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Characteristics of Perforated Appendicitis: Effect of Delay Is Confounded by Age and Gender

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Abstract
Introduction The effect of age and gender on time to perforation in acute appendicitis has not been well characterized. This study examined the relationship between duration of disease and appendiceal perforation in different subgroups of age and gender.
Methods This study is a retrospective analysis of 380 patients who underwent an appendectomy from January 2000 to June 2005 at a rural teaching hospital.
Results Factors associated with perforated appendicitis included age, symptom duration, CT scan, and distance from the hospital. Factors associated with increased patient time included age, temperature >101.5 F, and referral from an outside institution. Factors associated with shorter system time included right lower quadrant tenderness, classic or severe presentation, and leading diagnosis of acute appendicitis. Preoperative CT scan increased system time by approximately 3 h. Analyzing symptom duration and time to perforation, males have a higher prevalence of perforated appendicitis compared to females with similar duration of symptoms. In patients older than 55 years of age, 29% had perforated appendicitis at 36 h of symptoms and 67% at 36 to 48 h of symptoms. In a multivariate regression analysis, age greater than 55 years (odds ratio (OR) 3.0, *P* value 0.007), fever (OR 4.3, *P* 0.007), and symptom duration more than 24 h (OR 4.1, P 0.001) were significant predictors of perforated appendicitis.
Conclusions There is an early risk of perforated appendicitis even within the first 36 h of symptoms. This risk appears to be higher in males and patients older than 55 years, a quarter of whom are perforated within the first 36 h of symptom duration. Additionally, perforation in acute appendicitis may be more of a continuous phenomena worsening exponentially with duration of symptoms rather than a threshold phenomenon.

Keywords Timing · Operation · Appendectomy · Acute appendicitis · Perforated appendicitis · Delays · Waiting time

Introduction

The delay associated with the treatment of acute appendicitis can be broadly divided into patient-related delay and system-related delay. Patient delay in the form of late presentation to the hospital probably constitutes majority of the delay in the treatment of acute appendicitis.[1–7]

Recent studies in pediatric populations suggest that postponing appendectomy until daytime hours with fluids and antibiotic treatment is safe.[8–10] Similar analyses in adults have yielded mixed results with proponents of both initial nonoperative treatment[2, 11] as well as urgent appendectomy on diagnosis.[12] This decision, however, is best based on knowledge of the natural history of acute appendicitis. Published data from urban centers suggests that the risk of perforated appendicitis increases after 36 h of untreated symptoms.[13] However, there is evidence that this progression to perforated appendicitis varies with age and gender. For example, a significant proportion of elderly patients present with perforation or abscess formation.[14, 15] At present, it is not known whether this is due to late

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presentation of older adults to the hospital or an aggressive course of acute appendicitis. The effect of gender is less clear but may exist especially due to greater diagnostic delays in females.[16] Finally, whether rural versus urban residence, based on underlying differences in demographics, socio-economic status, and access to health care, influences progression of acute appendicitis has not been studied.[16]

With these issues in mind, this study looked at the factors associated with perforated appendicitis as well as patient delay and system delay in a rural population undergoing appendectomy. To further clarify the effect of age and gender on the progression of acute appendicitis to perforation, we did further analyses with the hypothesis that the rate of progression of acute appendicitis to perforation is different in subgroups of age and gender with older adults having a more rapid progression.

Material and Methods

This study is a retrospective analysis of all patients who underwent appendectomy at the Guthrie-Robert Packer Hospital (RPH) in Sayre, PA from January 2000 to June 2005. Robert Packer is a tertiary community teaching hospital with 240 beds that serves rural areas stretching over a 100-mile radius. The vast majority of patients undergoing appendectomies at this hospital are admitted through the emergency room (ER) where they are first seen by the ER physicians. Surgical consults are then obtained as deemed appropriate by the ER physician.

Initially, we identified all patients who underwent appendectomy at this institution during the above period. On a case by case basis, we then excluded patients who had an incidental or interval appendectomy. Of the 492 patients who underwent appendectomies during this time period, 45 patients were thus excluded. In order to obtain comparability to published studies of acute appendicitis, we then excluded all patients who had undergone a negative appendectomy.[13] There were 60 negative appendectomies during this period for a negative appendectomy rate of 13%. Seven patients with incomplete medical records were also excluded.

Patient Variables

Data were then collected on the remaining 380 patients. Chart review was done to collect information on patient demographics including age, gender, race, insurance, distance from the hospital based on the zip code of residence, relevant clinical history including comorbidities (diabetes mellitus, coronary artery disease, congestive cardiac failure, hypertension, or renal insufficiency or failure), radiological studies including CT scans, and pathology results. Age was analyzed both as a continuous and a categorical variable (<15, 15–45, 45–55, and >55 years). Since more than 97% of the patients in our population are Caucasians, the effect of race was not analyzed further. Patients for whom physicians noted appendicitis or acute abdomen with appendicitis as the leading diagnoses were considered to have a clinical impression of appendicitis. All other diagnoses were considered uncertain. Patients with five or more of the following clinical features were considered to have a classic presentation of appendicitis: (1) history of right lower quadrant pain; (2) anorexia; (3) nausea; (4) a temperature greater than 101.5 F; (5) right lower quadrant tenderness, guarding, or rebound tenderness; and (6) a white blood cell count (WBC) greater than 12,000/dL. Data on admission heart rate and dysuria were also collected. Patients with a classic presentation of appendicitis along with generalized abdominal tenderness were considered to have severe disease.

CT scan results were interpreted based on the final radiology report. CT scans at this institution are interpreted by an attending radiologist from 8 AM to 9 PM and by a consultant radiology service at night. All the consultant radiology reports are reinterpreted by an attending radiologist the next day for accuracy and quality assurance. In cases of ambiguity about reports, results were coded in consultation with an in-house attending radiologist. We categorized the findings on CT scan into normal appendix, acute appendicitis, and acute appendicitis with perforation. These were based on an internal consensus about the definitions to be used due to lack of a standard scale and the low sensitivity and specificity of CT scans for the diagnosis of perforated appendicitis.[17] Presence of periappendiceal fluid with or without extraluminal gas and/or loculated fluid collection with or without fluid level on the CT scan was used to classify perforated appendicitis.

All specimens were examined by an attending pathologist. The rate of perforated appendicitis was calculated based on all the appendectomies. A patient was defined to have perforated appendicitis if a perforation was noted by the pathologist, or if intraoperatively, the surgeon noted perforated appendicitis along with an abscess. There was a high correlation between the surgeon and the pathologist for the diagnosis of perforated appendicitis by the above definition (tetrachoric correlation coefficient 0.81, P value <0.0005).

Delay

The time between a patient's first notice of symptoms of fever, anorexia, nausea or vomiting, or abdominal pain and the time of registration in the ER were defined as "patient time". This was recorded in hours when the exact time of start of symptoms was available. When the exact time was not available, the nearest 12 h time was recorded. For example, "early morning" was approximated to 0600,

"evening" was approximated to 1800, and so on. Commonly, patients also noted the duration of symptoms in terms of half day increments. For example, the term "one day" was used by about 20% of patients to describe duration of symptoms. This was recorded as 24 h for the analyses. No particular age group or gender was noted to use such descriptive terms more often than other groups. The time from ER to the operating room was defined as "system time" and was coded in hours. ER arrival time was available from the ER registration sheet. For patients who had been referred for abdominal pain from outside facilities, system time was calculated with respect to the examination leading to the appendectomy. Time of surgery was available from the operating room documentation.

We also defined the "symptom duration" to perforation from the first start of symptoms. For this, we adjudicated the time of perforation for all patients. As there is no practical method to ascertain the exact time of perforation, we defined it to be the time of surgery for patients who did not have a preoperative CT scan suggesting perforated appendicitis. For patients who had evidence of perforated appendicitis on the preoperative CT scan which was confirmed operatively or postoperatively, the time of the CT scan was used as the time of perforation. There were 15 patients who had a preoperative CT scan suggesting perforated appendicitis and evidence for the same operatively or postoperatively. Symptom duration was analyzed as a categorical variable (<12 h, 12 to 24 h, 1 to 1 1/2 days, 1 1/2 to 2 days, 2 to 4 days, 4 to 8 days and >8 days). The data for calculation of symptom duration was not available for 31 patients (8% of the total population, 12 patients with perforated appendicitis).

Statistical Analysis

Statistical analysis was performed using STATA (Version 10, College Station, TX, USA). Bivariate associations were evaluated using chi-square tests for pairs of normally distributed ordinal variables. Many of the variables were not normally distributed. We used the Wilcoxon rank-sum test and Kruskal–Wallis equality-of-populations rank test to examine differences in central tendency for these variables. The Wilcoxon rank-sum test and Kruskal–Wallis equality-of-populations rank test are nonparametric tests that can be used to compare medians in populations that are comparably but not necessarily normally distributed.[18–20] The P value for trend was calculated using a logistic regression model with perforated appendicitis as the outcome variable and time periods of symptom duration as the independent variable. A P value less than 0.05 would indicate a significantly increased risk of perforated appendicitis with increasing symptom duration. Logistic regression was also used to assess the risk of perforated appendicitis while controlling for other independent variables. The study was approved by the Institutional Review Board at the Robert Packer Hospital.

Results

Clinical Characteristics and Perforation

There were 380 patients who underwent an appendectomy for acute appendicitis. Eighty-one (21%) patients were found to have perforated appendicitis. Median age for the overall population was 30 years. Patients with perforated appendicitis were significantly older that the group with no perforation. There was no difference in gender distribution between the two groups. On physical exam, patients with perforated appendicitis were noted to have a significantly increased prevalence of right lower quadrant tenderness and dysuria compared to the nonperforated group. There was no difference in abdominal pain, nausea or vomiting, diarrhea, anorexia, or mean heart rate, temperature, or WBC count between the two groups. Patients found to have perforated appendicitis underwent CT scans significantly more often than patients who were found not to have a perforation. Seventeen patients (28%) with perforated appendicitis were noted to have evidence for the same on CT scan. Patients with perforated appendicitis had a significantly longer patient time (60 vs. 33 h, $P<0.005$). The mean duration of symptoms prior to ER presentation for the entire population was 38.5 h. There was no significant difference in system time between the two groups. Patients with perforated appendicitis were noted to live farther from the hospital compared to the nonperforated group. Although statistically significant, this result is unlikely to be a clinically significant difference. There was no significant difference in place of first examination or insurance status between the two groups. As expected, the length of stay was significantly longer for patients with perforated appendicitis (Table 1).

Factors Associated with Patient Time

Patients older than 45 years of age were noted to have a significantly longer patient time. There was no significant difference based on gender, insurance status, anorexia, nausea or vomiting, or peri-umbilical pain. Patients with temperature more than 101.5 F on presentation had a significantly longer patient time probably reflecting advanced disease on presentation. Distance from the hospital did not influence patient time. Patients who were first examined outside of the RPH ER were noted to have a significantly longer patient time. Additionally, patients who underwent CT scans on admission were also noted to have a significantly longer patient time, suggesting that patients

Table 1 Patients' characteristics based on the presence or absence of rupture

Variable	Overall *N*	Nonperforated appendicitis	Perforated appendicitis	*P* value
N (%[a])	380	299 (79)	81 (21)	
Mean age (median; range[b])[c,d]	34 (30; 6–79)	31 (26; 7–79)	44 (50; 3–81)	<0.005
Women, *N* (%)[e]	149 (39)	121 (40)	28 (35)	0.34
Clinical exam, *N* (%)[e]				
Abdominal pain	377 (99)	297 (99.3)	80 (98.7)	0.61
RLQ tenderness	194 (51)	146 (49)	48 (59)	0.03
Nausea/vomiting	262 (69)	202 (68)	56 (69)	0.97
Diarrhea	38 (10)	26 (9)	12 (15)	0.10
Anorexia	241 (63)	190 (63)	51 (63)	0.39
Dysuria	14 (4)	8 (3)	6 (7)	0.04
Median heart rate (range)[e]	88 (48–144)	87 (47–144)	90 (60–145)	0.15
Mean temperature (range)[e]	98.8 (95.1–104.4)	98.8 (95.7–104.4)	99.2 (95.1–104)	0.06
Mean WBC count (range)[e]	14.5 (3–36)	14.6 (4.9–28.1)	14.5 (3–25.3)	0.45
CT scan, *N* (%)[e]				
Performed	221 (58)	161 (54)	60 (74)	<0.005
Perforated appendicitis	26 (11)	9 (5.5)	17 (28)	<0.005
Mean delay in hours (median; range)[c,d]				
Patient time	38.5 (24; 2–336)	33.2 (24; 2–336)	60 (48; 1.5–336)	<0.005
System time	9.8 (6.5; 0.7–92)	10 (6.5; 0.4–113)	8.9 (6.5; 0.8–76)	0.82
Mean distance from hospital in miles (median; range)[c,d]	21 (19.5; 1–86)	20 (19; 1–86)	24 (21.5; 1–89)	0.04
First examined, *N* (%)[e]				
RPH ER	257 (68)	208 (70)	49 (60)	
Outside RPH ER	117 (31)	88 (29)	29 (36)	0.21
Medicaid or self pay, *N* (%)[e]	84 (22)	68 (23)	16 (20)	0.92
Mean length of stay (median; range)[c,d]	2.9 (2; 0–15)	2 (1; 0–10)	6 (5; 0–27)	<0.005

All patients with negative appendectomies have been excluded

RLQ right lower quadrant, *RPH* Robert Packer Hospital, *ER* emergency room

[a] Percentages are a percent of the column total for whom the condition was recorded. The percentages may not add up to 100 due to patients with missing information

[b] Range is the 1st to the 99th percentile

[c] Based on Wilcoxon rank-sum test

[d] Median and mean values are reported for variables that are not normally distributed

[e] Based on chi-square

with longer duration of symptoms may preferentially undergo CT scans at this institution (Table 2).

Factors Associated with System Time

Clinical characteristics associated with significantly shorter system time included right lower quadrant tenderness, classic or severe presentation of acute appendicitis, and leading diagnosis of acute appendicitis. Duration of symptoms more than 36 h, age, gender, insurance, heart rate, or temperature did not significantly influence the system time. Patients first examined in the RPH ER had a significantly longer system time, probably reflecting the need for further workup compared to patients referred from outside institutions. Patients undergoing preoperative CT scan had significantly longer system time by 2.6 h compared to those who did not (Table 3).

Effect of Age, Gender, and Delay on Symptom Duration

Figure 1 shows the rate of perforation in the overall population at various intervals of symptom duration. In the overall population, percent perforated steadily increased from 7% at less than 12 h to 42% at 2–4 days. Thus, of the total 211 patients with a symptom duration of 36 h or less 9% were noted to have perforated appendicitis. Figure 2 compares the perforation rates based on gender. Males had a shorter symptom duration to perforation compared to

Table 2 Time from start of symptoms to registration in the RPH ER: patient time

Characteristics	Number	Mean patient time (median; 1st–99th percentile)	*P* value
Age (years)			
≤15	70	35 (24; 2–336)	
15–45	177	34.5 (24; 2–336)	
45–55	51	48.6 (36; 3–168)	
>55	51	47 (24; 1.5–336)	0.006
Gender			
Male	215	38 (24; 2–168)	
Female	134	39.4 (24; 3–336)	0.57
Insurance			
Medicaid or self pay	84	40 (24; 1–336)	
Other insurance	265	33.2 (24; 2–336)	0.34
Temperature (°F)			
≤101.5	307	36.4 (24; 2–336)	
>101.5	21	49.6 (36; 12–168)	0.009
Anorexia			
No	53	50.3 (24; 1–336)	
Yes	227	34.8 (24; 2–168)	0.38
Nausea or vomiting			
No	106	41.5 (24; 1.5–336)	
Yes	243	37.2 (24; 3–336)	0.87
Peri-umbilical and RLQ pain			
No	235	42.8 (24; 2–336)	
Yes	105	28.5 (24; 3–144)	0.31
Distance from the hospital			
Less than 20 miles	184	37 (24; 1.5–336)	
More than or equal to 20 miles	165	39.8 (24; 3–336)	0.25
Location of first examination			
RPH ER	239	30.2 (24; 2–168)	
Outside RPH ER	108	56.9 (24; 4–336)	<0.005
CT performed			
No	147	32.2 (24; 2–336)	
Yes	202	43.1 (24; 2–168)	0.05

**P* values are based on the Kruskal–Wallis equality-of-populations rank test for age and Wilcoxon rank-sum test for the other variables

females. Eleven percent of males present with perforated appendicitis in the first 36 h of symptoms as opposed to 6% of females; 31% of males and 19% of females presenting between 36 to 48 h were noted to have perforated appendicitis. Figure 3 compares patients less than or equal to 55 years to patients aged more than 55 years. For the patients aged more than 55 years, we combined the less than 12-h and 12- to 24-h time intervals due to the small number of patients in these groups. We also combined the 4- to 8-day and the more than 8-day time intervals for the above reason. Twenty-nine percent (7 out of 24) of patients aged older than 55 years have perforated appendicitis within 36 h of symptoms as opposed to 7% (13 out of 188) of patients aged 55 years or less. After 36 h, there is a steady increase in the percent perforated in the less than 55 age group and a dramatic increase in percent perforated in the more than 55-year age group. Seventy-one percent of patients older than 55 years with symptoms for 36 to 48 h had perforated appendicitis. Figure 4 compares the perforation rates between males and females in the less than 55-year-old age group. Again, males perforate sooner than females, with 8.5% of males (10 out of 117) having perforated appendicitis within 36 h of the start of symptoms as opposed to 4% of females (3 out of 71). These trends were noted to be significant in all the groups except the 55 years and older. We think that the nonsignificant *P* value for the 55-year and older group may be due to both the higher rate of perforation on presentation as well as the small number of patients in each interval of symptom duration. In all time periods of symptom duration, we noted a gradual increase in the percent of perforated appendicitis rather than a threshold effect. In a multivariate logistic regression model, age more than 55 years (odds ratio 3.0, *P* value 0.007), elevated temperature >101.5 F (odds ratio 4.3, *P* value 0.007), and symptom duration more than

Table 3 Time from registration in the ER to surgery: system time

Characteristic	Number	Mean system time (median; range)	*P* value*
Age (years)			
≤15	71	8.5 (6.6; 0.65–29.9)	
15–45	180	9.9 (6.2; 0.35–126.9)	
45–55	52	9 (6.7; 0.9–75.7)	
>60	52	8.9 (6.8; 0.8–113)	0.68
Gender			
Male	218	9.2 (6.2; 0.7–46)	
Female	137	10.7 (6.8; 0.7–113)	0.16
Insurance			
Medicaid or self pay	84	8.7 (6.3; 0.3–127)	
Other insurance	271	10.2 (6.6; 0.7–92)	0.22
Heart rate			
<100	231	9 (6.5; 0.7–40)	
≥100	96	12 (6.7; 0.9–127)	0.22
Temperature (°F)			
>101.5	21	7.8 (6.6; 1–26)	
≤101.5	308	9.3 (6.5; 0.7–64)	0.65
Right lower quadrant tenderness			
No	167	12.2 (6.8; 0.4–127)	
Yes	182	7.6 (6; 0.7–39)	0.01
Classic presentation			
No	228	10.4 (6.7; 0.7–76)	
Yes	127	8.8 (6.0; 0.7–127)	0.01
Symptoms more than 36 h			
No	247	8.7 (6.6; 0.6–35)	
Yes	102	10.3 (6.4; 0.8–76)	0.59
Severe presentation			
No	107	8.7 (5.4; 0.7–127)	
Yes	19	9.7 (9.8; 1.4–23)	0.01
Leading diagnosis a/c appendicitis			
No	43	15.7 (12.5; 0.8–137)	
Yes	306	9.1 (6.3; 0.7–64)	<0.005
Location of first examination			
RPH ER	239	10 (7.2; 1.5–64)	
Outside RPH ER	112	9.5 (3.9; 0.4–113)	<0.005
CT performed			
No	149	8.3 (4.5; 0.4–113)	
Yes	206	10.9 (8.0; 0.8–76)	<0.005

**P* values are based on the Kruskal–Wallis equality-of-populations rank test for age and Wilcoxon rank-sum test for the other variables

24 h (odds ratio 4.1, *P* value 0.001) were significant predictors of perforated appendicitis (adjusted for age, gender, heart rate >100, temperature >101.5 F, admission CT scan, insurance, distance, and symptom duration).

Discussion

In an analysis of patients undergoing appendectomy for acute appendicitis in a rural population, we found that (1) CT scans significantly contribute to system delays in the treatment of acute appendicitis. (2) Delay in presentation, age more than 55 years, and elevated temperature (>101.5 F) on admission are predictors of perforated appendicitis. (3) There is an early risk of perforation even within the first 36 h of start of symptoms which may be higher in males than females. Additionally, patients older than 55 years of age have a 29% prevalence of perforated appendicitis in the first 36 h from start of symptoms. (4) Rather than a threshold effect, we noted a gradual increase in the percent of perforated appendicitis in all time periods of symptom duration.

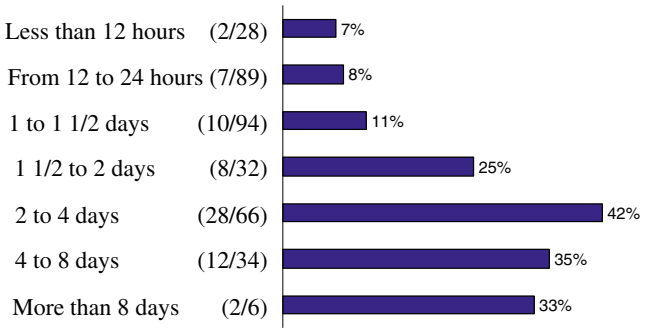

Fig. 1 Graph showing symptom duration (*X* axis) and percentage perforated (*Y* axis). The *numbers in parentheses* are the total number of patients with perforated appendicitis over the total number of patients undergoing appendectomy in that respective time interval

Previous authors have suggested that the risk of perforated appendicitis is relatively small in the first 36 h of symptom onset.[13, 21] Bickell et al. also noted that the risk of perforation increases by 5% for each ensuing 12-h period after 36 h. Our study found an increasing incidence of perforated appendicitis starting at even less than 12 h of duration of symptoms. We explored the reasons for this discrepancy. The rate of perforated appendicitis in our study is higher compared to the above study but is comparable to studies from other US centers.[12] Our adjudication of symptom duration was different from the studies in the past. For patients with perforated appendicitis on whom a preoperative CT scan demonstrated the same, we used time of CT scan to indicate time of perforation.[12, 13] To address possible selection bias due to different quantification of symptom duration for patients with CT scans, we analyzed the symptom duration in all 15 patients where perforation was noted on the preoperative CT scan. We next compared this time to the usual definition of symptom duration based on the time of surgery. All but one patient were noted to have the same classification of time period of symptom duration. So our adjudication of symptom duration probably does not explain our results. The median age of our population is higher than the study by Bickell et al. Another influential study by Ditillo et al. found that there was an increasing incidence of "G3 pathology" (perforated appendicitis or phlegmon) with increasing total interval to surgery starting at less than 12 h of untreated symptoms.[12]

To explore the effect of age and gender on our findings, we performed multiple sub-analyses. The authors are unaware of previous studies exploring these relationships. Our results summarized above suggest a more aggressive natural history of acute appendicitis in the elderly population as well as possible differences between males and females. Previous research has suggested that a significant proportion of the elderly present with perforation or abscess formation.[14, 15] This has been suggested to be due to delay in presentation in previous analyses. We, however, noted a comparable patient time and system time for patients older than 55 years compared to younger patients. Thus, underlying physiological differences may be a better explanation for rapid perforation in older adults. This assertion has also been suggested historically.[22] Another mechanism that may partly explain the finding of earlier perforation in males and older adults may be differences in perception of pain. Studies have noted females to be at higher risk for clinical pain syndromes and also have more severe postoperative and procedural pain.[23] Similarly, older patients have also been noted to have atypical presentations with lower incidence of right lower quadrant guarding and pain.[24]

This study also brings out interesting differences and similarities between urban and rural populations presenting with acute appendicitis. Robert Packer Hospital is located in Sayre, PA with a population of about 5,500 and outside urbanized areas as defined by the United States Census Bureau in 2000.[25] Although Robert Packer Hospital is a tertiary referral hospital serving a large geographic region that includes urbanized areas, patients with acute appendicitis are generally cared for in local hospitals within those urbanized areas. Recent papers have suggested that the major delay in acute appendicitis is the pre-hospital delay in presentation rather than the system time after presentation to the hospital.[11–13] Our study confirms this finding in a rural population. Although CT scans caused the major

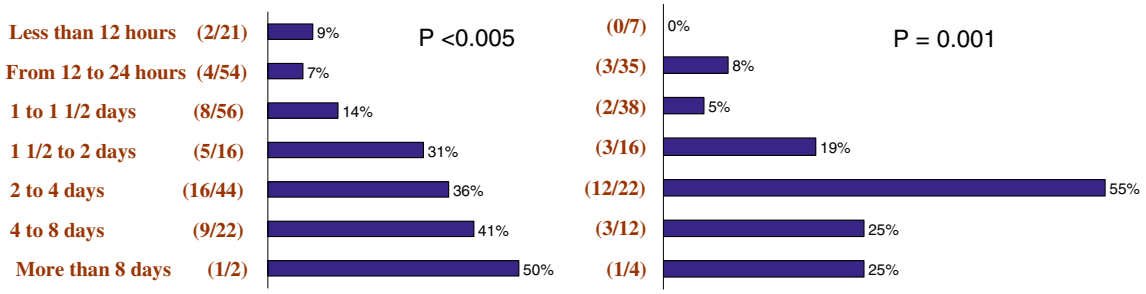

Fig. 2 Graph comparing the relationship between symptom duration (*X* axis) and percentage perforated (*Y* axis): males and females. The *numbers in parentheses* indicate the total number of patients with perforated appendicitis over the total number of patients undergoing appendectomy during the respective time interval. *P* value for trend of percent perforated appendicitis based on symptom duration

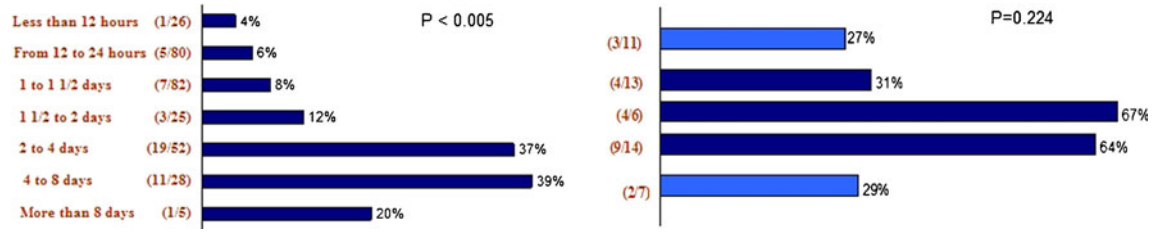

Fig. 3 Graph comparing the relationship between symptom duration (*X* axis) and percentage perforated (*Y* axis): age 55 years or less and age more than 55 years. The *numbers in parentheses* indicate the total number of patients with perforated appendicitis over the total number of patients undergoing appendectomy during the respective time interval. *P* value for trend of percent perforated appendicitis based on symptom duration. For the patients aged 55 years or above, we combined the less than 12-h and 12- to 24-h time intervals as well as the 4- to 8-day and the more than 8-day time intervals due to the small number of patients in these groups

system delay in our study, the delay was less compared to studies from urban centers where it was noted to be as high as 10 h.[13, 26, 27] In a recent paper from this center, CT scans were noted to be associated with an increased risk of perforated appendicitis especially in males.[16] This study provided additional evidence of the mechanism based on increased system time. At our institution, we have continued to implement the policy of surgical consultation before CT scan in males younger than 45 years of age presenting with a leading diagnosis of acute appendicitis. We could not find a recent study providing mean symptom duration prior to presentation for patients in the USA. This is about 38 h for our population. Our study population is mostly Caucasians as compared to urban centers where the population includes a higher percentage of minority groups. We also found that the ratio of males to females in our population is higher than the urban population.[28] We did not find any recent paper reporting distance from the hospital. We did not find any relation between insurance status and perforation in our population. This is also different from urban populations where there might exist a difference in perforation rates based on insurance status.[29, 30]

The retrospective determination of the time of start of symptoms continues to be a significant limitation of this paper. We do, however, believe that our data on symptom duration are not confounded by knowledge regarding the final patient outcome. This was because these data were collected separately by an independent data collector with no knowledge of final patient outcome. Our results are also consistent across all age groups and genders and similar to previously published literature.[2, 12, 13] Insufficient data on adults older than 55 years of age in our dataset limited our analysis of the effects of delay in this age group. Being a mostly Caucasian population, the effects of race also cannot be analyzed in our population.

Our study confirms the relationship between symptom duration and advanced pathology in patients with acute appendicitis in a rural population. We additionally also found varying trends in the rate of perforation based on the age and gender of the patient population. This finding has important treatment and policy implications. Appendectomy should be performed without delay in adults especially males and those older than 55 years once diagnosis is confirmed. The system delays in management of acute appendicitis can be decreased by prudent utilization of CT scans.

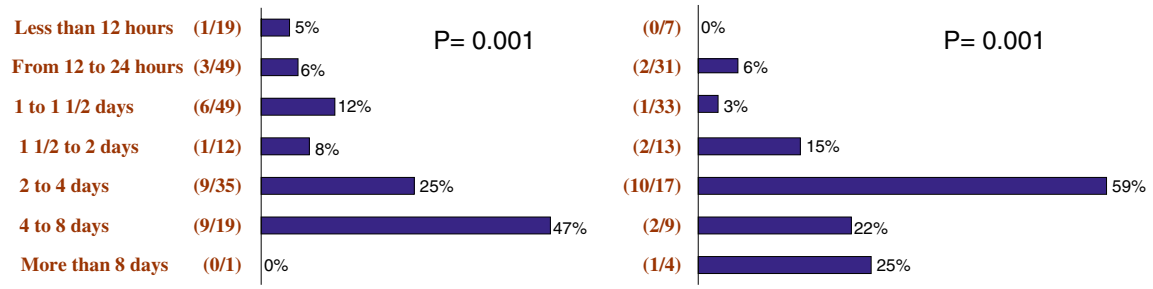

Fig. 4 Graph comparing the relationship between symptom duration (*X* axis) and percentage perforated (*Y* axis): males and females less than or equal to 55 years of age. The *numbers in parentheses* indicate the total number of patients with perforated appendicitis over the total number of patients undergoing appendectomy during the respective time interval. *P* value for trend of percent perforated appendicitis based on symptom duration

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CASE REPORT

Extraabdominal Lymph Node Metastasis in Gastrointestinal Stromal Tumors (GIST)

Nikolaos Vassos · Abbas Agaimy · Werner Hohenberger · Roland S. Croner

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Abstract
Background The two principal ways of metastases in gastrointestinal stromal tumors (GISTs) are diffuse intraabdominal spread and liver metastasis whereas lymph node metastases (LNM) are extremely rare. Accordingly, nodal dissection is generally not recommended for GISTs' surgical treatment.
Methods We present two unique cases of GIST with synchronous and metachronous extraabdominal LNM, whose clinical, macro-/microscopic, and immunohistochemical criteria, surgical and neo- or adjuvant therapy were investigated in retrospective analysis.
Results A 76-year-old man was presented with an inguinal mass and a simultaneously detected intraabdominal mass. Pathological evaluation of the core needle biopsy from the inguinal lymph node confirmed metastatic GIST. Partial resection of the ileum and inguinal lymph node dissection (LND) showed a spindle cell GIST in the ileum with inguinal LNM. Imatinib mesylate therapy was administered, which was interrupted 2 years later because of patient's intolerance. A 35-year-old man underwent extended gastrectomy, atypical liver resection, splenectomy, and LND because of a huge gastric fundus GIST. Postoperative imatinib mesylate therapy was administered. Histology showed multiple regional lymph node metastasis. Two years later, a left hemihepatectomy was performed for liver metastases. During follow-up, new axillary LNM were detected, and a sunitinib therapy was initiated. Thereafter, he developed progressive axillary, mediastinal, hepatic, abdominal, osseous, and cutaneous metastases, and he was treated by palliative cytoreductive surgery.
Conclusion These two cases demonstrate that extraabdominal node metastasis may rarely occur in GIST, either initially or in the setting of widespread disease. In selected cases with confirmed or suspected LNM, LND should be considered. Metachronous extraabdominal lymph node metastasis represents a late event in high-risk GISTs and cannot be controlled by drug therapy alone.

Keywords GIST · Gastrointestinal stromal tumor · Lymphatic metastasis · Lymph node

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract.[1,2] They differentiate similar to the gastrointestinal (GI) pacemaker cells, the interstitial cells of Cajal.[3] GISTs may show as either spindled or epithelioid cells or a combination thereof.[4,5] They differ from other non-epithelial digestive tract tumors, including leiomyomatous and neurogenic tumors, on the basis of specific histological and immunophenotypic features that permit diagnosis. The recognition that activating c-kit mutations play a central role in the pathogenesis of GISTs and the recent development of clinically effective inhibitors targeting the transmembrane

receptor tyrosine kinase c-kit radically changed the management of advanced and metastatic disease. However, surgery is still the only curative treatment for resectable primary GISTs without evidence of metastasis.[6] The two main routes of GIST metastases are intraperitoneal dissemination and hematogenous spread to the liver. GIST metastasis to other visceral organs, lungs, pleura, bones, or brain is rare.[7] Lymph node metastasis is unusual (1–2%), thus, routine lymphadenectomy is not recommended.[8–10] However, rare cases with nodal spread are documented in the literature,[11–17] which were detected accidentally intra-abdominally during surgery. Doubtless, extraabdominal lymphogenic spread is exceptionally rare and appears to herald a worse prognosis.[18,19] Herein, we present the clinical course and the histopathological characteristics of two cases of GIST with synchronous or metachronous extraabdominal lymph node metastases.

Case 1

A 76-year-old man was diagnosed with a large abdominal mass during the diagnostics for severe melena that necessitated a blood transfusion. His previous medical history revealed terminal renal insufficiency, arterial hypertension, intermittent arrhythmia with atrial fibrillation, hypercholesterolemia, cirrhosis of the liver, splenomegaly, and diverticulitis of sigmoid. An ulcer in the jejunum was already diagnosed outwards. The clinical examination revealed a palpable abdominal mass in the lower abdomen. Laboratory tests were within normal limits aside from the hemoglobin (5.8 g/dl) and the creatinine value (5.5 mg/dl). Ultrasonography showed a non-homogeneous hypoechoic mass with cystic and solid components occupying the left lower abdomen as well as one smaller tumor in the right groin. An upper GI endoscopy revealed no pathological findings. A magnetic resonance tomography (MRT) confirmed this huge intraabdominal mass, 15×15×20 cm in size and showed at the same time ascites, pleural effusion, left adrenal adenoma, and suspicious inguinal lymph node (Fig. 1). An ultrasonography-guided inguinal needle biopsy was performed, and the histopathologic report revealed lymph node metastasis of a GIST (Fig. 2). After the preoperative examinations, a laparotomy was performed. A hemorrhagic tumor was found in the left lower abdomen, arising from the ileum. Notably, no other visible tumors were detected along the intestinal tract and the peritoneum. The tumor mass was removed en bloc by segmental resection of the ileum (ca. 15 cm), and a dissection of the mesenteric lymph nodes was performed. At the same time, the known left adrenal adenoma was removed, and a dissection of the left inguinal lymph nodes was performed. Resection margins were macroscopically free of disease. On the fifth postoperative day, a cardioversion was performed because of atrial flutter. The patient was discharged on the seventh postoperative day with stable cardiac and pulmonary conditions. The histological specimen showed a large (ca. 16 cm) cellular spindle (partially epitheloid) gastrointestinal stromal tumor of the ileum with a high mitotic activity (35 mitoses per 50 high-power fields). The inguinal lymph node metastases showed similar histology. Both the ileal tumor and the metastasis showed a strong CD117 and CD34 immunoreactivity, but no actin, desmin, or S-100 expression. The proliferation rate was under 5%. The microscopic resection margins and the mesenteric lymph nodes that were resected were free of disease. According to these findings, the tumor corresponded to a high-risk GIST with synchronous extraabdominal lymph node metastasis. Hence, an adjuvant imatinib mesylate therapy was initiated, which was interrupted 5 months later, restarted 2 months later for 5 months, and then completely stopped by the patient because of intolerance. He died 30 months postoperatively of dilatative cardiomyopathy.

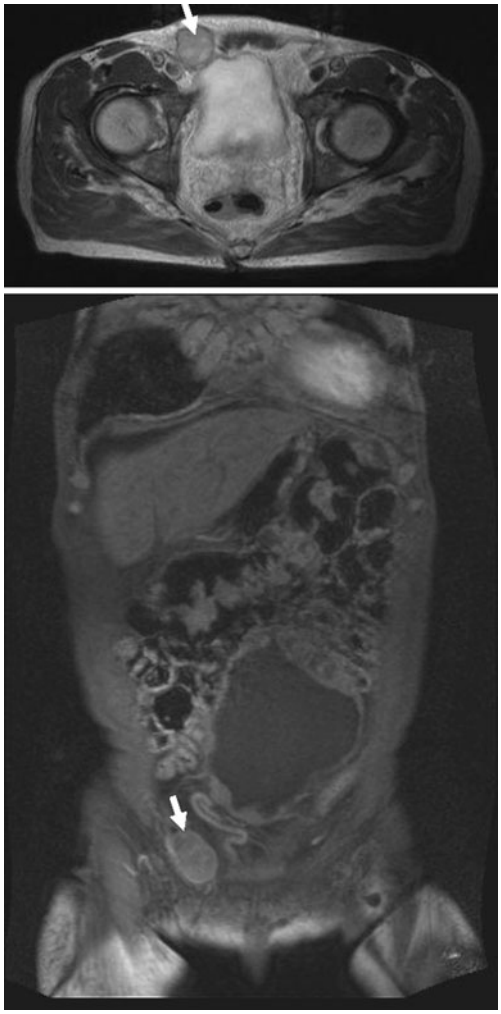

Fig. 1 Identification of inguinal lymph node metastasis from abdominal GIST by MRI

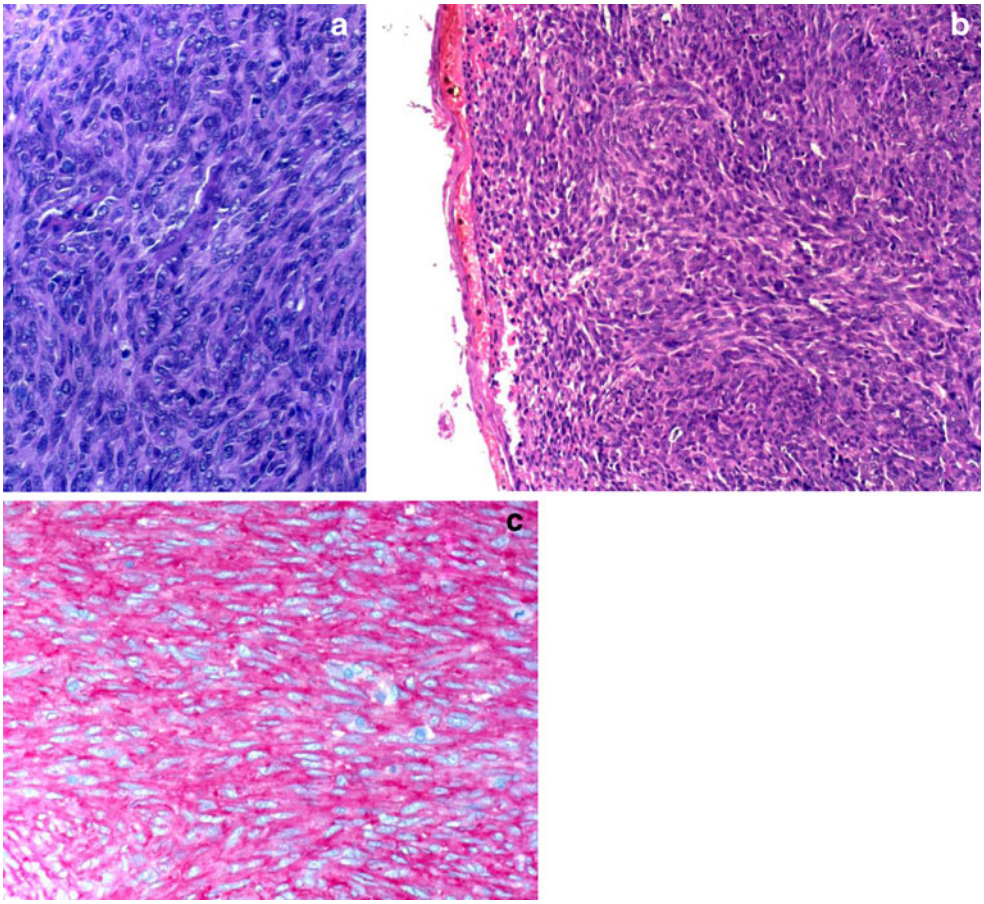

Fig. 2 H&E staining of the primary abdominal GIST (**a**) and the corresponding synchronous inguinal lymph node metastasis (**b**) (note dilated congested subcapsular sinus on the *left*). CD117 staining of the inguinal lymph node metastasis (**c**)

Case 2

A 35-year-old man with upper abdominal symptoms and gastrointestinal bleeding without history of pre-existing diseases was found to have a large ulcerated gastric mass in the stomach diagnosed during gastroscopy. An explorative laparotomy was performed and revealed a huge tumor (15×10 cm) in the large curvature of the stomach (fundus) and a smaller one (5×6 cm) in the small curvature of the stomach. Intraoperative metastases in the liver (segment III, VI, and other smaller ones) as well as lymph node involvement in the celiac trunk and in the splenic hilum were detected. The metastases of the liver were histologically confirmed. A gastrectomy with Roux-Y reconstruction with corresponding lymphadenectomy and a splenectomy was performed, but no synchronous resection of the liver was done. The postoperative specimen showed histologically a mixed (epithelioid–spindled) GIST of the stomach with regional lymph node metastases. The immunohistochemical examination revealed strong CD117 and focal CD34 expression but no reactivity with actin, desmin, and S-100 protein. The tumor corresponded to a high-risk GIST with synchronous regional lymph node and liver metastases. After the operation, the patient started an adjuvant imatinib mesylate therapy. He remained initially with no tumor progress, but 3 years later, a computed tomography as well as an MRT showed progression of the liver disease (segment IVa, V, VIII), and a left hemihepatectomy was performed. Histological examination showed viable metastatic GIST. Because of hepatic metastasis progress under imatinib mesylate therapy, the drug was stopped, and a thermoablation of a metastasis in segment IVa of the liver was performed. During the follow-up 50 months later, right axillary lymph node metastases were diagnosed via positron emission tomography, and a sunitinib therapy was initiated, under which a resolution of the tumor was detected. However, 62 months later, there was a clear progress of the disease with axillary, mediastinal, hepatic, abdominal, osseous, and cutaneous metastases. A palliative axillary lymph node dissection and an en bloc tumor exstirpation of the abdominal wall metastasis were performed. The histological findings showed GIST metastases with strong CD117 and CD34 reactivity and a proliferation rate of 20%. Despite the continued sunitinib therapy, the patient died of the disease 74 months after the first diagnosis.

Discussion

The two principal ways of metastases in GIST are diffuse intraabdominal spread and hematogenous dissemination to the liver.[1,20] Metastases rarely develop in lymph nodes,

bones, soft tissues, and skin and extremely rarely in brain and lungs.[21] Thus, lymphadenectomy is seldom necessary for GIST treatment in contrast to adenocarcinomas of the gastrointestinal tract. However, there is limited experience with management of GISTs with lymphatic metastasis. Regarding the need for lymphadenectomy, many investigators claim that GISTs rarely metastasize to lymph nodes, even in high-risk cases.[22] Accordingly, nodal dissection is generally not recommended for GISTs during surgical treatment. However, lymph node dissection should be considered in patients with any suspicion of nodal metastasis intraoperatively or after histopathological verification.[20,23]

In our patients, we performed a lymphatic dissection because of the preoperative or intraoperative awareness of the lymph node metastases. In the first patient, the inguinal lymph node metastasis was diagnosed preoperatively, and in the second patient, enlarged regional lymph nodes were noticed during the first operation. These synchronous nodal metastases contributed to the decision of the adjuvant imatinib mesylate treatment. Most of the reported GISTs with lymphatic spread occurred in intraabdominal nodes.[8,9,11] In this report, we described two unusual cases: one with multiple synchronous intraabdominal lymph node metastasis followed by multiple metachronous extraabdominal node metastasis. The other patient presented with isolated synchronous extraabdominal inguinal lymph node metastasis; he showed no evidence of further metastasis until his death of cardiac failure 30 months later. According to the National Institutes of Health risk classification for GISTs,[22] both of the presented tumors belong to the high-risk group, and according to the grading system for GIST after surgical resection,[12] both of them were classified as high-grade GIST due to the presence of one major and three minor unfavorable prognostic factors. To our knowledge, only a single case of GIST metastatic to inguinal lymph node was reported during preparing this manuscript. Zhang et al. described the case of inguinal node metastasis occurring 3 years after resection from high-risk gastric GIST that showed synchronous liver metastasis. Thus, their case was similar to the clinical course in our second case. Accordingly, our first case represents the first report of GIST presenting with isolated synchronous inguinal lymph node metastasis. Thus, GIST must be included in the differential diagnosis of spindle cell lesion encountered in extraabdominal lymph nodes.

Conclusion

In conclusion, we presented two unique cases of GISTs with synchronous and metachronous extraabdominal lymph node metastases. Although extraabdominal lymph node metastasis generally represents a late event in GIST's natural history and is not compatible with long-term survival, one of our cases with isolated initial inguinal node metastasis showed an uneventful course, and the patient has experienced no disease recurrence until his death 30 months later. Histopathological criteria for selecting patients who might benefit from nodal dissection are still lacking.

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CASE REPORT

Non-Operative Management of Right Posterior Sectoral Duct Injury Following Laparoscopic Cholecystectomy

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Abstract
Objective The purpose of this study is to describe the outcomes of conservative management for patients with right posterior sectoral bile duct injury acquired during laparoscopic cholecystectomy.
Methods This retrospective, consecutive case series reviews seven patients with an isolated injury to the right posterior or right hepatic duct occurring during laparoscopic cholecystectomy.
Results Seven patients with an isolated right sectoral duct injury were studied, six women and one man aged 22 to 71 years (mean age, 43.6 years). Diagnosis of bile duct injury occurred between 1 day and 13 weeks after the initial cholecystectomy. Three patients had plastic biliary stents placed and six patients had JP drains placed. All patients in this series were managed conservatively, with no reoperation for formal repair of the bile duct. Length of follow-up ranged from 2 to 14 months (mean, 8.2 months). At last follow-up, all patients were asymptomatic with no biliary drainage.
Conclusions Conservative management is an important option for patients with an isolated right posterior bile duct injury.

Keywords Bile duct · Bile duct injury · Iatrogenesis · Cholecystectomy · Laparoscopic cholecystectomy

Introduction

Iatrogenic bile duct injury is a major cause of morbidity and mortality following laparoscopic cholecystectomy, occurring in 0.5–1.4% of cases.[1] The presence of variant biliary anatomy increases the risk of such injuries. Prior studies have estimated that 19–39% of the population have anatomic variations of the biliary tree.[2,3] These aberrant ducts can be mistaken for the cystic duct and clipped or cauterized inadvertently.

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The most common biliary anomaly, occurring in 4–8% of patients, is an aberrant insertion of the right posterior duct into the biliary tree, usually inserting close to the cystic duct (Fig. 1).[2–4] Intraoperatively, it can be mistaken for the cystic duct and injured, either in isolation or in conjunction with the "classic" bile duct injury, where the common bile duct is mistakenly clipped.[5,6] This low-lying duct provides the only drainage for hepatic segments 6 and 7. As such, injury to the right posterior sectoral duct can present with biliary fistula, biloma, abdominal pain, or peritonitis.[1,6–11] Many patients, however, remain asymptomatic, and it is likely that the frequency of this type of injury is underreported.[7,8]

An isolated right posterior bile duct injury presents a unique challenge for two key reasons. First, diagnosis is often elusive, as endoscopic retrograde cholangiopancreatography (ERCP) can be read as normal in the setting of continued bile leak or biloma.[9,10] Second, while classic bile duct injury has a conventional repair (the Roux-en-Y hepaticojejunostomy), in this non-classic injury the treatment of choice is not well defined. With limited literature and experience to guide therapy for this injury, many surgeons do routinely perform Roux-en-Y in order to reattach the right posterior system.[6,9,12]

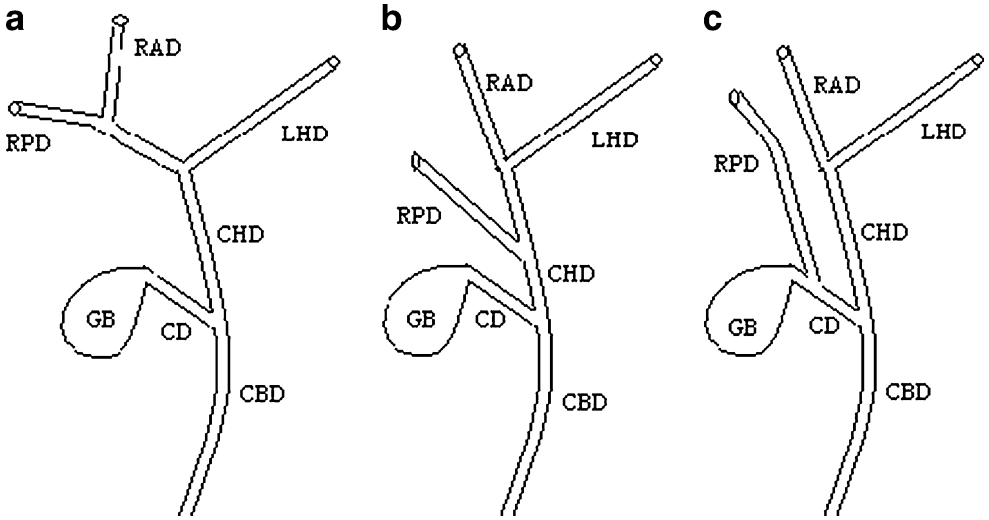

Fig. 1 Variations in right posterior duct anatomy. *CBD* common bile duct, *CD* cystic duct, *GB* gallbladder, *CHD* common hepatic duct, *LHD* left hepatic duct, *RPD* right posterior duct, *RAD* right anterior duct. **a** Normal hepatic ductal anatomy, **b** low insertion of RPD into CHD, and **c** insertion of RPD into CD

Herein, we present a case series of seven consecutive patients referred to our institution over a 3-year period with isolated injury to a right hepatic posterior sectoral duct. All seven patients were managed conservatively with drains and stent placement but without reoperation for bile duct repair. These patients have had full recovery with complete symptom resolution and no clinical or radiological evidence of continued bile leak or cholangitis.

Materials and Methods

The patients in this series were referred to the senior author (JMS) on the hepatobiliary surgery service at Emory University Medical Center in Atlanta, GA for evaluation and treatment of a suspected or known bile duct injury. The patients had previously undergone laparoscopic cholecystectomy in the 3-year period between August 2006 and August 2009. A retrospective review of all clinical documents was performed, including hospital and outpatient visit records and radiology images.

Results

Patient Demographics

This study includes seven consecutive patients with an injury to the right posterior hepatic duct; six women and one man aged 22 to 71 years (mean, 43.6 years). Patient characteristics and details of presentation and diagnosis are outlined in Table 1.

Presentation and Diagnosis

Bile duct injury was discovered in one of three fashions that will be discussed separately. Two patients had suspected injuries intraoperatively. In one case, a bile leak was

Table 1 General patient information

Age (year)/ sex/race	Initial procedure[a]	Presentation with bile duct injury	Diagnostic modality	Time from cholecystectomy to diagnosis	Final diagnosis[b]
55/F/C	LC converted to open	Bile drainage	CT fistulogram	8 weeks	RPD injury
27/F/H	LC	RUQ pain	Intraoperative cholangiogram	0 days	RPD injury
53/F/C	LC converted to open	Bile drainage	MRCP	6 weeks	Right hepatic duct injury
71/M/C	LC	Asymptomatic	MRCP	3 weeks	RPD injury
36/F/AA	LC	Biloma, jaundice, RUQ pain, N/V	ERCP	3 weeks	RPD injury
22/F/C	LC	Bile drainage	MRI	1 day	RPD injury
41/F/C	LC	Biloma, RUQ pain	MRCP	13 weeks	RPD injury

F female, *M* male, *C* Caucasian, *H* Hispanic, *AA* African American, *LC* laparoscopic cholecystectomy, *RUQ* right upper quadrant, *CT* computed tomography, *MRCP* magnetic resonance cholangiopancreatography, *RPD* right posterior sectoral duct

discovered shortly after ligation and transection of the cystic duct. The surgeon unsuccessfully attempted an ERCP, placed a right upper quadrant Jackson-Pratt (JP) drain prior to closing, and transferred the patient to our center. Magnetic resonance imaging (MRI) demonstrated that the bile leak was due to an isolated right posterior duct injury. The second intraoperative diagnosis was identified on intraoperative cholangiogram as a right posterior ductal injury (Fig. 2). The surgeon placed a clip on the injured duct and placed a JP drain.

The other five patients presented ambulatory within 2 weeks of the initial cholecystectomy. Identification of the anatomic location of the ductal injury was made using various modalities, including ERCP, MRCP, and CT fistulogram (Fig. 3). Three patients presented with continued percutaneous bilious output from JP drains, without biloma or other symptoms. The remaining two patients presented with biloma and right upper quadrant pain, one of whom had accompanying chills, diaphoresis, nausea/vomiting, and jaundice. Final diagnosis for six patients was an isolated right posterior sectoral duct injury; one patient had a right hepatic duct injury (Table 1).

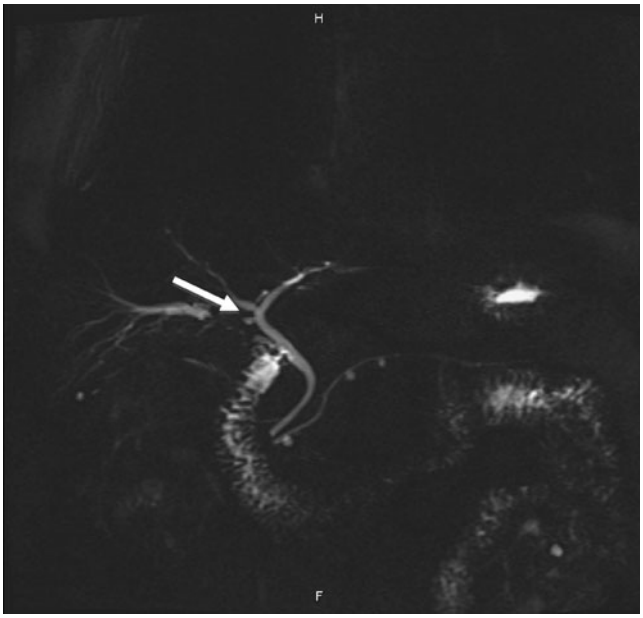

Fig. 3 Magnetic resonance cholangiopancreatography showing clipped cystic duct with a low-inserting right posterior duct stump (*arrow*)

Management and Follow-Up

All patients were managed conservatively, with no reoperation for bile duct repair. Five patients had JP drains placed intraoperatively; the remaining two patients had drains placed postoperatively at the time of diagnosis with bile duct injury (Table 2). All patients received complete follow-up by one hepatobiliary surgeon. In three cases, patients received plastic biliary stents to mitigate local inflammation should they proceed with subsequent biliary repair. These patients, however, became asymptomatic during this initial period and did not undergo the planned surgical repair. In the remaining four cases, patients were given the options of Roux-en-Y hepaticojejunostomy, segmental hepatectomy, or waiting with repeat blood tests and imaging for spontaneous resolution.

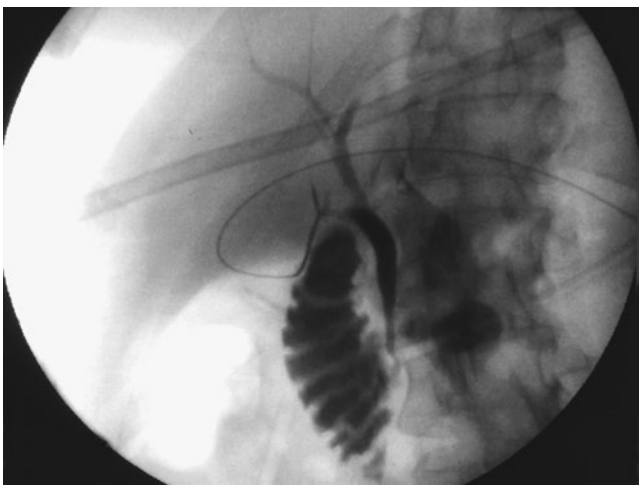

Fig. 2 Intraoperative cholangiogram demonstrating a filling defect in the right posterior sectoral system

Ultimately, all patients experienced complete symptom resolution on follow-up. JP drains were removed between 1 and 16 weeks postoperatively. In two patients, the drains were advanced slowly over the course of several weeks. Drainage at time of removal was less than 20 cm^3/day for all patients. Magnetic resonance imaging in all patients was either normal or showed some degree of atrophy of the right posterior liver with compensatory hypertrophy of the left segments (Fig. 4).

Follow-up was complete and ranged from 2 to 14 months, with an average duration of 8.2 months (Table 3). All patients were asymptomatic at their last clinic visit. Two patients had no complaints and thus no clinical indication for laboratory evaluations at follow-up visits. After IRB approval, multiple attempts were made to contact these patients to document normalization of liver enzymes; however, it was not possible to reach either patient.

Discussion

Anomalous right posterior sectoral ducts represent the most common anatomic variant of the biliary tract (Fig. 1). Ligation of this duct, which provides the only drainage to hepatic segments 6 and 7, can lead to bile leak or biloma and present with pain, cholangitis, or peritonitis. This

Table 2 Details of clinical management

Age (year)/ sex/race	Drain placed[a]	Initial volume of bile drainage	Bile drainage at drain removal	Time until removal of drain	Management of drain prior to removal
55/F/C	Intraop	>30 cm^3/day	5 cm^3/day	9 weeks	Drain slowly withdrawn
27/F/H	Intraop	0 cm^3/day	0 cm^3/day	1 week	None
53/F/C	Intraop	300 cm^3/day	10 cm^3/day	6 weeks	None
71/M/C	Intraop	Not recorded	<5 cm^3/day	1 week	None
36/F/AA	1 week, replaced at 4 weeks	>500 cm^3/day	10–20/day	7 weeks	Drain slowly withdrawn
22/F/C	Intraop	200 cm^3/day	0 cm^3/day	8 weeks	None
41/F/C	13 weeks	Not recorded	Not recorded	16 weeks	None

F female, *M* male, *C* Caucasian, *H* Hispanic, *AA* African American, *Intraop* intraoperatively

[a] All drains referred to are Jackson-Pratt drains

anatomic variant is of considerable interest, both due to an increased likelihood of injury during cholecystectomy and because this type of injury presents a diagnostic and therapeutic challenge.

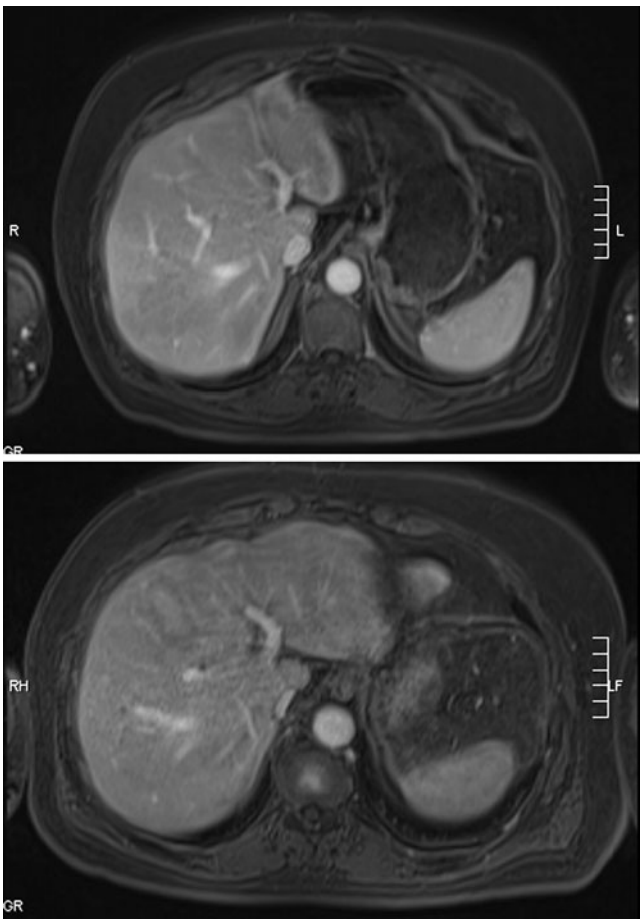

Fig. 4 Venous phase magnetic resonance imaging demonstrating hypertrophy of left lower and middle segments at 12 months after initial operation (*bottom image*) when compared with image from the same patient at 2 months after initial operation (*top image*)

In the present series, we found excellent outcomes with conservative management. This approach to right posterior duct injury represents a change in our practice. This change began as an unintended consequence of the circumstances surrounding the first two cases of the series. The first patients were offered operative repair; however, due to lack of insurance approval in one case and insurance coverage in the other, both patients delayed full evaluation after the original laparoscopic cholecystectomy. In both cases, pain and biliary drainage had resolved with normalization of liver function tests before an operative repair could be scheduled. Consequently, these patients were offered conservative treatment with the possibility of performing right partial segmentectomy of the liver in the event of recurring symptoms. As both patients remained asymptomatic, conservative management became the treatment of choice for isolated right posterior duct injuries in our practice.

There are numerous reports of right-sided bile duct injuries that advocate for a variety of therapies. Meyers et al. reported 14 cases of injury to an aberrant right sectoral duct, either in conjunction with a classic injury or in isolation.[6] In the isolated right posterior duct injuries, three had biliary symptoms and underwent Roux-en-Y repairs. The remaining four patients were sent home for an attempt at spontaneous closure; two patients were successful and the other two continued to have high-output fistulae and underwent Roux-en-Y of the solitary duct. Christensen et al. described five patients with ligation of an aberrant right hepatic bile duct at cholecystectomy.[11] Four of these patients were treated with Roux-en-Y repair and one with partial hepatectomy.

In others reports, management strategy is secondary—with Roux-en-Y reconstructions almost a given—as they focus on the diagnostic dilemma posed by right posterior duct injury. Usually, these case reports describe patients presenting months after surgery with continued symptoms, often with a biloma, in the face of a normal ERCP.[6,7,9–11] In

Table 3 Follow-up and recovery

Age (year)/ sex/race	Length of follow-up (months)	Lab values at last follow-up[a]		
		Alkaline phosphatase (U/L)	Aspartate aminotransferase (U/L)	Alanine aminotransferase (U/L)
55/F/C	2.3	n/a	n/a	n/a
27/F/H	12.8	n/a	n/a	n/a
53/F/C	13.7	145	26	28
71/M/C	6.6	64	23	31
36/F/AA	8.1	90	23	19
22/F/C	4.2	138	44	60
41/F/C	9.8	206	35	37

F female, *M* male, *C* Caucasian, *H* Hispanic, *AA* African American, n/a not applicable

[a] Laboratory reference ranges: alkaline phosphatase, 32–92 U/L; aspartate aminotransferase, 15–41 U/L; alanine aminotransferase, <34 U/L

such patients, the placement of a drain to evacuate the biloma led, in each case, to significant symptom resolution. Lillemoe et al. described nine patients with isolated right segmental duct injury, focusing mainly on the diagnostic challenge these injuries present.[9] After correct diagnosis was made via percutaneous cholangiography, percutaneous biliary stents were placed which led to prompt resolution of all signs of biliary sepsis. Our report tallies with the Lillemoe's description, as the patients presented here also experienced symptom resolution with proper drainage of bile. In the Lillemoe series, however, after allowing time for biliary drainage, all nine patients underwent scheduled Roux-en-Y hepaticojejunostomy.

No operative management is without risk. Studies of operative management for bile duct injury report complication rates of up to 43%.[12] Reports of isolated right posterior duct repairs tend to be case studies of small numbers of patients, but development of anastomotic stenosis following Roux-en-Y is a common feature, occurring in up to 33% of patients.[9,10] Accordingly, to limit iatrogenesis, if the conservative approach is successful, it ought to replace operative management.

Conservative management and spontaneous resolution in this injury appears in the literature as early as 1935. A case report described a patient who underwent surgery for a choledochal cyst in which the right hepatic duct was ligated.[13] The patient remained asymptomatic for years. At a subsequent abdominal operation, the surgeons noted that the right lobe of the liver had atrophied, with compensatory hypertrophy of the left lobe.[13,14] This atrophy/hypertrophy complex mirrors the MRI findings in our patients.

Most importantly, the conservative approach is supported by the benign natural history of an isolated right posterior duct injury. Strasberg et al. categorize the problem of injury to a sectoral duct as resulting in either obstruction (type B injury) or bile leak (type C injury).[8] For occlusive injuries, they comment that these patients are often asymptomatic and that the undrained hepatic segment generally experiences atrophy with compensatory hypertrophy of the remaining portions. Should the patient become symptomatic, however, they continue to advocate hepaticojejunostomy or segmental hepatic resection.

Bile duct injury has been a significant complication of cholecystectomy since its inception, and the problem has become more common in the advent of laparoscopic surgery.[5,15] The classic bile duct injury, transection of the common bile duct, results in a loss of connection between the biliary and enteric systems. The classic repair is a Roux-en-Y hepaticojejunostomy to reconnect the biliary tract and allow for bile drainage.

Isolated sectoral duct injuries present a different problem than common bile duct injury. The biliary system remains connected to the duodenum, and only a section of the liver is left without proper drainage. To reconnect this hepatic section, a Roux-en-Y procedure is often performed. Other options that have been reported include induced atrophy or surgical resection of the involved liver segment.[1,8] Reports of patients managed without surgery are rare in the literature. Some case series of bile duct injuries require operative management as part of their inclusion criteria.[15] Reports that do consider spontaneous resolution generally do so only for asymptomatic patients.[8,12] In our experience, six of the seven patients we describe presented with biliary symptoms, ranging from bile leak to biloma and cholangitis, and still underwent successful conservative management.

Many questions still remain in determining the appropriate treatment algorithm for this type of injury. Severity of symptoms, the volume of liver drained by the transected duct, and presentation with leak versus stricture all certainly come into play when deciding the most appropriate course of action. Finally, patient preference can also play a role in deciding whether to attempt a definitive operative treatment or allow time for the injury to heal spontaneously. A prospective case series is required to confirm our findings and better assess the role each of these factors plays in choosing a treatment plan. In the meantime, the current report draws attention to a sometimes neglected option in the

surgical literature: the possibility of conservative management as a first line treatment for symptomatic patients.

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MULTIMEDIA ARTICLE

Robotic-Assisted Laparoscopic Side-to-Side Lateral Pancreaticojejunostomy

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Keywords Puestow · Pancreaticojejunostomy · Robotic

Introduction

Side-to-side lateral pancreaticojejunostomy is commonly used to treat chronic pancreatitis. It is usually performed via a laparotomy due to the technical challenges of constructing a pancreatico-enteric anastomosis laparoscopically. The robotic system offers improved visualization and dexterity in fashioning such a complex anastomosis.

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Case Description

A 58-year-old veteran was diagnosed with a gallstone-induced chronic pancreatitis and malnutrition due to intractable abdominal pain. The patient had previously undergone laparoscopic cholecystectomy. Preoperative ERCP revealed an obstructing pancreatic duct stone in the head of the pancreas with associated upstream duct dilatation. The patient had failed multiple attempts to access and stent the pancreatic duct, including unsuccessful cannulation of the minor papilla. Pancreatic protocol CT scan demonstrated a well-developed pseudocyst in communication with the dilated pancreatic duct. The video explains in details the operative steps. He was discharged home on POD #4. There were no complications during his hospitalization and at 6 months follow-up.

Conclusion

Robotic-assisted laparoscopic side-to-side lateral pancreaticojejunostomy is feasible and safe. The robot system offers the advantage of a true three-dimensional view based on a double optical system, in addition to a wide range of freedom of motion, which contributes to the feasibility of this advanced laparoscopic suturing.

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HOW I DO IT

Stapling Technique for Performing Billroth II Anastomosis After Distal Gastrectomy

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Abstract The circular stapling technique has been widely applied for gastrointestinal anastomosis in gastrectomies (open or laparoscopic) for distal gastric cancers. We describe this method for use in performing Billroth II anastomosis in distal gastrectomies. From 2002–2009, we report the results following the use of the circular stapling technique performed in 520 patients at a single institution. The median time of completing the anastomosis was shorter using the stapling technique compared to the hand-sewn technique. The use of the stapler resulted in two cases of minor intraluminal bleeding at the anastomotic site. The circular stapling method can be applied safely and more efficiently in performing Billroth II reconstruction after distal gastrectomy compared to the hand-sewn method in patients with gastric cancer.

Keywords Stomach neoplasm · Gastrectomy · Gastrojejunostomy · Surgical stapling

Introduction

The mechanical stapler has been used in most gastrointestinal anastomoses. There have been many reports examining the use of circular staplers in Billroth I anastomosis but only few studies reporting the use of circular staplers in Billroth II anastomosis.[1,2] The application of the circular stapler has been shown to result in shorter operating time and more secure anastomosis. This study was conducted in patients with distal gastric cancer who underwent open and laparoscopic distal gastrectomy with Billroth II anastomosis using the circular stapler. In this report, we illustrate the use of the circular stapler technique in Billroth II anastomosis.

Technique

We make an upper midline incision and perform an omentectomy. The first portion of the duodenum is freed to ensure adequate room for insertion of the 60-mm linear stapler (TA60; Auto Suture Co, Norwalk, CT) and perform the duodenal transection inferior to the pylorus. After transection of the duodenum, we support the staple line using 4-0 polyglactin (Vicryl; Ethicon, Inc., Cincinnati, OH) seromuscular sutures (Fig. 1a). The left gastric vessels are ligated and lymph node dissection is performed. After ligating and dividing the vessels of the greater and lesser curvatures, we apply a straight Allen clamp on the side of the greater curvature near the lower pole of the spleen for transection. The Allen clamp is applied on the side of the lesser curve near the proximal two thirds of the stomach for transection. Microscopically, cancer-free resection margins for EGC is at least 3 cm and at least 5 cm for AGC. The distal stomach is then resected with a 100-mm linear stapler (GIA100; Autosuture Co., Norwalk, CT; Fig. 1b). The

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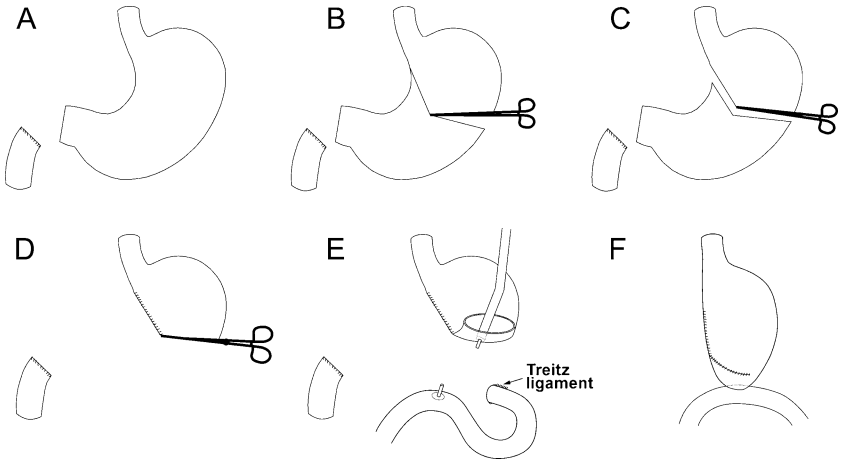

Fig. 1 Simplified and streamlined illustration of the anastomotic technique

location of the tumor lesion is confirmed and the proximal and distal resected margins are identified from the removed specimen and subsequently sent for frozen section. We use the long pin forceps to gently hold the jejunal wall including the mucosa and a segment that is 20 cm distal to the Treitz ligament, and a reusable purse-string clamp is applied below the forceps. The anvil is inserted into the opening of the jejunum and the purse-string around purse-string notch of the anvil is tightened. Once the frozen section confirms negative margins, we release the Allen clamp and make an opening in the greater curvature. The circular stapler (EEA25; Auto Suture Co., Norwalk, CT) shaft is inserted into the opening of the greater curvature and the knob is twisted to extend the trocar in order to perforate the posterior wall of the stomach (Figs. 1c and 2a). After the anvil is conjoined with the trocar, fully tighten, fire, and then maintain a firm squeeze of the handle for 10 s. Finally, we close the opening of the greater curvature using the 60-mm linear stapler to successfully complete the gastrojejunostomy (Fig. 1d).

Results

Since June 2002, we have employed a mechanical stapling technique instead of the traditional hand-sewn anastomosis in Billroth II anastomosis following distal gastrectomy. We have performed this reconstruction technique for the last 8 years in 520 patients. None of the 520 patients experienced anastomotic leaks or stenotic complications. There have been two cases with minor intraluminal bleeding at the anastomotic site. These two patients recovered fully without additional operative interventions and were discharged with satisfactory oral intake.

We compared the stapling technique to the hand-sewn technique by examining the operating time and the cost in nine cases. The median time in performing the anastomosis with the stapling technique was 03 min 43 s (02:43–04:21)

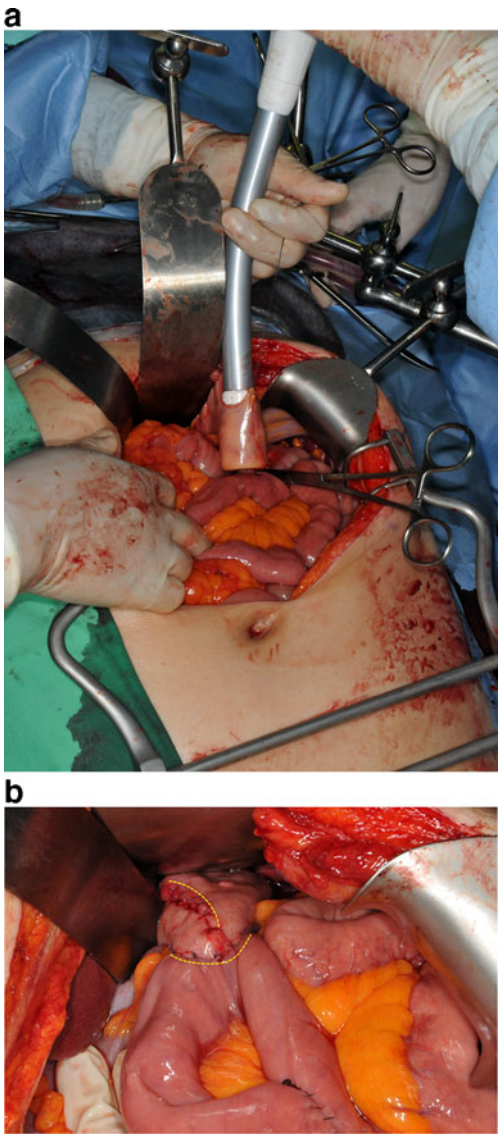

Fig. 2 **a** EEA stapler is inserted through the opening of greater curvature and combined with the anvil, then approximated. **b** Seromuscular suturing at the anastomotic line is performed and the anastomosis is completed. Linear and circular stapled lines do not meet

compared to 14 min 43 s (12:26–16:45) with the hand-sewn technique. The stapler technique added an additional cost of 481,600 W ($430.00) for the stapler.

Discussion

The stapling technique has widely been used to perform gastrointestional anastomosis during gastrectomy (open or laparoscopic) for distal gastric cancer. This technique has also been effectively used for Billroth II anastomosis.

Our gastrointestinal reconstruction technique for gastrojejunostomy has several advantages over others. (1) Prior to performing the reconstruction, the distal stomach containing the main lesion was removed. Previous studies have reported manipulation of the stomach without prior resection of the mass containing portion of the distal stomach.[3,4] However, our technique allows us to confirm complete resection of the tumor as well as tumor-free margins by freezing the section prior to proceeding with the anastomosis. (2) By using the 25-mm circular stapler, the likelihood of traumatic injury to the jejunum would be less. (3) Upon firing the stapler, we maintain maximal squeeze for 10 s. This step improves hemostasis and decreases the rate of postoperative bleeding at the anastomotic site. Furthermore, we are able to inspect the inner aspect of the anastomosis through the greater curvature. (4) Finally, because the linear and circular stapled line do not meet, this method using the one circular–one linear stapler technique improves vascular supply compared to the two linear stapler method (Fig. 2b). Therefore, the rate of anastomotic leak, necrosis, and stricture may be less. This demonstrates a successful Billroth II reconstruction.

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HOW I DO IT

Single Incision ("Scarless") Laparoscopic Total Abdominal Colectomy with End Ileostomy for Ulcerative Colitis

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Abstract
Introduction Total abdominal colectomy with ileal pouch–anal anastomosis is the intervention of choice for patients with medically uncontrolled ulcerative colitis. A three-stage approach is preferred in particularly debilitated patients. In this setting, laparoscopic surgery has shown to be safe, offering several advantages over the open approach. Single incision laparoscopic surgery is a new minimally invasive approach which represents a true scarless procedure for the first step of the restorative proctocolectomy. In this article, we describe our technique in performing the single-incision total abdominal colectomy.
Methods The single-access device is inserted through a circular incision made at the ileostomy site, which was marked preoperatively. The procedure is performed with conventional laparoscopic instruments through one 12-mm and three 5-mm trocars introduced in the single-access device gel platform. Good exposure of the operating field is obtained by changing the Trendelenburg position and the lateral tilting of the table. We start the operation by mobilizing the right colon, then proceeding clockwise to the rectosigmoid junction. The ileocolic pedicle is divided after the visualization of the right ureter and duodenum. The right colon is mobilized in the medial-to-lateral fashion. The hepatocolic ligament is taken down, and the transverse mesocolon and the greater omentum are divided to mobilize the transverse colon. Subsequently, the lateral attachments of descending colon are taken sharply, and the avascular line of Toldt is bluntly dissected. Under direct visualization of the left ureter, the inferior mesenteric vein and the branches of the sigmoid arteries are identified, dissected, and divided. After switching to a 5-mm laparoscope, the rectosigmoid junction is divided with an endoscopic stapler. The specimen is exteriorized, and the terminal ileum is divided extracorporeally. Finally, the ileostomy is matured in the standard Brooke fashion.
Conclusion Between May and November 2010, we performed ten single-incision total abdominal colectomies, all completed successfully without complications or need of conversion, with a mean operative time of 139±24 min and an estimated blood loss of 100±120 ml. The postoperative course was unremarkable in all cases, with prompt return of bowel activity and short postoperative stay. In our experience, single-incision total abdominal colectomy has shown to be a safe alternative to standard laparoscopy in selected patients and appears to be a promising technique with the potential to improve short-term outcomes.

Keywords Laparoscopic surgery · Ulcerative colitis · Surgical technique

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Introduction

Laparoscopic colorectal surgery has been shown to have several advantages over the conventional open approach, including shorter hospital stay, faster return of bowel function, decreased postoperative pain, wound complications and adhesion formation, and better cosmetic results.[1–3] In our practice, laparoscopic surgery has become the preferred approach to ulcerative colitis over the years.[4] Traditional laparoscopy still requires multiple incisions for placement of

the trocars and specimen extraction that affects cosmesis, particularly important in a young patient population, as it is in ulcerative colitis.[5]

New surgical strategies have been proposed in the effort to avoid or limit the number and size of skin incisions, such as natural orifice transluminal endoscopic surgery (NOTES)[6,7] and single incision laparoscopic surgery (SILS).[8,9] Although NOTES has the advantages of a true "no scar" procedure, using transgastric, transvaginal, and transrectal access to the abdominal viscera, the need for expensive specialized equipment and additional training has hindered the widespread acceptance of this approach. Currently, only reports of hybrid colectomies (combined laparoscopic and transluminal approach) have been reported.[10]

In the field of colorectal surgery, some reports have already been published on SILS surgery for both benign and malignant diseases.[7,11–17] Nevertheless, the acceptance of SILS for surgical management of ulcerative colitis patients has been quite slow, probably due to the magnitude of the procedure and the general poor medical condition of the patients. Particularly, in the setting of total abdominal colectomy (TAC), the SILS approach represents a true "no scar" procedure, using the site of the temporary end ileostomy as the abdominal access point. In this report, we describe the technical details of our approach to single incision laparoscopic total abdominal colectomy with end ileostomy for medically uncontrolled ulcerative colitis.

Methods

The indication for total abdominal colectomy in ulcerative colitis is typically medically refractory ulcerative colitis on aggressive medical therapy. These patients are typically managed in conjunction with our gastroenterology colleagues, part of our multidisciplinary inflammatory bowel disease team. In our practice, laparoscopic surgery is the approach of choice, preferring a three-stage procedure (TAC with an end ileostomy, followed by a restorative proctectomy with the ileo pouch anal anastomosis with a loop ileostomy, and finally, the ileostomy closure) for the more complex and debilitated patients. Patients are chosen for a SILS approach based on their body habitus, absence of significant associated comorbidities, and absence of previous abdominal surgery. At the time of surgery, typically, patients are on corticosteroids, with or without the concomitant use of immunomodulators.

Preoperative Care

The site of the future temporary end ileostomy in the right lower quadrant is marked preoperatively by a specialized wound and ostomy care nurse. Surgery is performed under general anesthesia with epidural analgesia, for postoperative pain control and intraoperative reduction of intestinal distension. All patients undergo mechanical bowel preparation the day before the procedure and rectal irrigation on the operating table. Antibiotic and antithrombotic prophylaxes are administered before the start of the procedures, with a stress dose of corticosteroids.

The patients are placed in lithotomy position with the legs slightly bent, abducted in stirrups, and both arms alongside the body. Pneumatic compression stockings are used for deep venous thrombosis prophylaxis. An orogastric tube and urinary catheter are placed after induction of anesthesia.

Equipment

In all cases, a GelPoint® Advanced Access Platform (Applied Medical, Rancho Santa Margarita, CA) was employed as sole access to the abdominal cavity. Its GelSeal® cap provides additional outer working space and the ability to achieve tissue triangulation even with the standard laparoscopic instrumentation that we routinely use. One 12-mm and three 5-mm self-retaining trocars are introduced through the gel platform in a Latin cross-shaped manner, with the 12-mm camera trocar placed at the extremity of the longer arm. After the induction of the pneumoperitoneum, the trocars float above the skin plane, maximizing the outer working space over a flexible fulcrum for a wide range of motion in the intraabdominal compartment in all planes.

Aside from the single-access device, the procedures are performed with conventional laparoscopic instruments. We use 5 mm straight (i.e., non-articulated) operating instruments, except for the endoscope (a 12-mm laparoscopic camera with a 30° lens, Karl Storz, Tuttlingen, Germany) and for the stapler (a 12-mm roticulated EndoGIA Universal loaded with 45-mm, 3.5-mm EndoGIA Roticulator stapler cartridges, Covidien Autosuture, North Haven, CT). Tissue dissection and vascular resection are performed using a 5-mm ENSEAL® Tissue Sealing Device (Ethicon Endo Surgery Inc., Cincinnati, OH).

Operative Procedure

Access, Exploration, and Exposure

A circular incision at the level of the previously marked ileostomy site is performed. Access to the abdominal cavity is gained dissecting through the subcutaneous tissue down to the fascia under direct vision. The anterior rectus sheath is opened longitudinally, and the rectal muscle fibers are retracted. The posterior rectus sheath is opened longitudinally. Through that opening,

the GelPoint device is inserted. The 12-mm trocar for the camera plus three 5-mm trocars are placed through the GelSeal. After the exploration of the abdominal cavity to assess the feasibility of the procedure, we start the dissection from the right colon, then proceeding clockwise, thus allowing us to first address the most difficult part (being just below the access site), and therefore the part at greater risk of conversion.

Right Colon Dissection

The operating table is placed in Trendelenburg position and tilted to the left in order to shift the small bowel on the left side and out of the pelvis, thus obtaining a good exposure of the right lower quadrant (Fig. 1). With the operator on the left side of the patient, the GelPoint is oriented in order to have the optical port in medial position (Fig. 1). The ENSEAL is introduced through the cephalic trocar. A laparoscopic grasper is used to retract the cecum upward and laterally, thus placing the ileocolic pedicle under tension. After having visualized and avoided the right ureter and the duodenum, the ileocolic pedicle is identified, dissected, and divided with the ENSEAL device (Fig. 1).

Medial to lateral submesenteric mobilization of the ascending colon is then completed all the way up to hepatic flexure, bluntly dissecting down the avascular plane between the colonic mesocolon and Gerota's fascia (Fig. 2). The lateral attachments are incised all the way down to the terminal ileum which is mobilized to allow construction of a tension-free end ileostomy, and the small bowel mesentery is divided all the way to the bowel for transection of the terminal ileum when extracting the specimen.

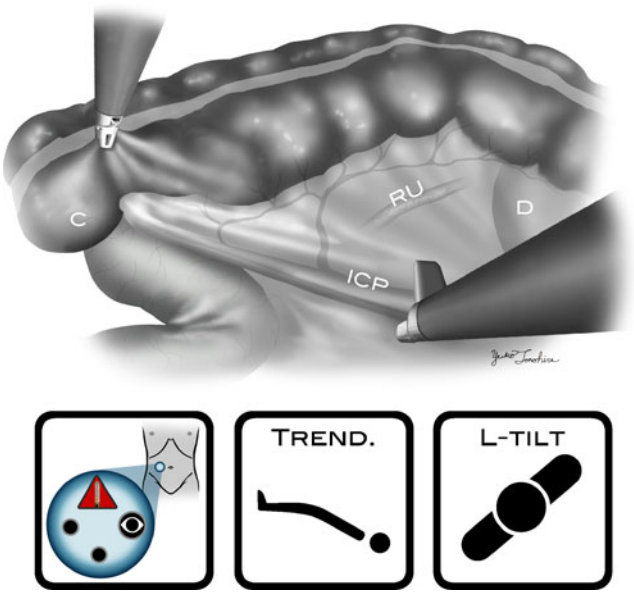

Fig. 1 Ileocolic pedicle (*ICP*) exposure and transection. The cecum (*C*) is retracted laterally. The right ureter (*RU*) and the duodenum (*D*) are visualized as well. In the *inserts*: GelPoint disposition with the optical port medial and the ENSEAL cranial. The table is tilted to the left side and in Trendelenburg position

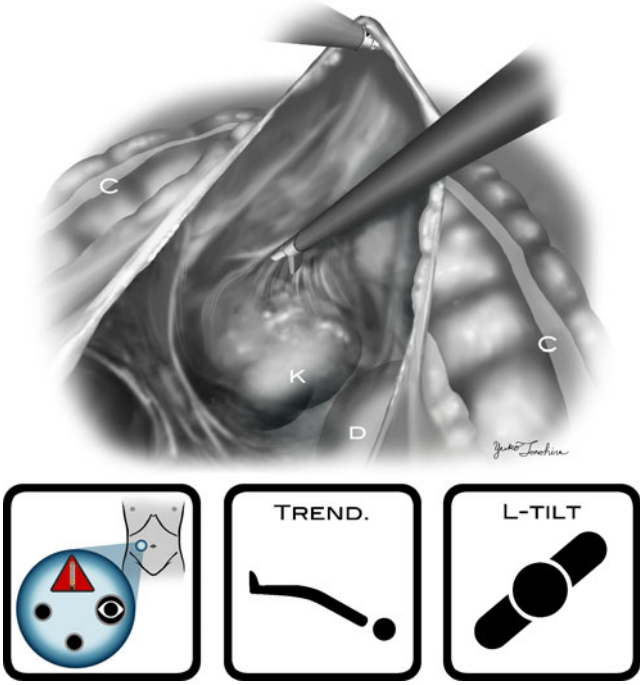

Fig. 2 Mobilization of the hepatic flexure. The ascending colon (*C*) is dissected in the avascular plane between mesocolon and Gerota's fascia, with visualization of the right kidney (*K*). *D* duodenum. In the *inserts*: GelPoint disposition with the optical port medial and the ENSEAL cranial. The table is tilted to the left side and in Trendelenburg position

Hepatic Flexure and Transverse Colon Dissection

The patient is placed in the reverse Trendelenburg position, and the operator moves between the legs of the patient. With a grasper retracting the hepatic flexure caudally and medially, the hepatocolic ligament is divided with the ENSEAL inserted through the caudal port. At this point, the table is tilted in a right lateral decubitus position to displace the small bowel, with the operator on the right side of the patient. The access device is turned 180°, and the transverse colon is mobilized by sequentially dividing the greater omentum just distal to the gastroepiploic arcade and the transverse mesocolon, with visualization of the pancreatic tail and, eventually, the left kidney (Fig. 3). The removal of the omentum en bloc with the specimen significantly facilitates this part of the operation. It is our practice to remove the omentum en bloc with the specimen in both open and laparoscopic assisted TAC.

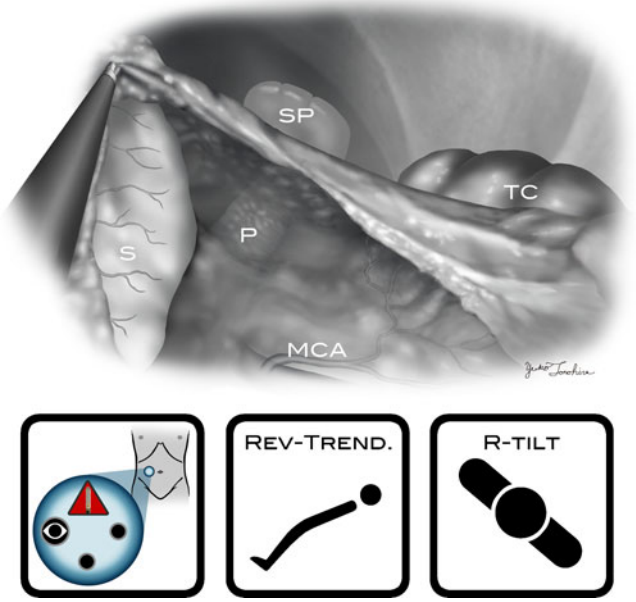

Fig. 3 Transverse colon (*TC*) mobilization by sequential division of the greater omentum, with visualization of the pancreatic tail (*P*). *S* stomach, *MCA* middle colic artery, *SP* spleen. The stomach is retracted superiorly to place the omentum under tension. In the *inserts*: the GelPoint is turned 180° to bring the optic laterally. The ENSEAL stays in the cranial position. The table is moved to a reverse Trendelenburg position and right-tilted

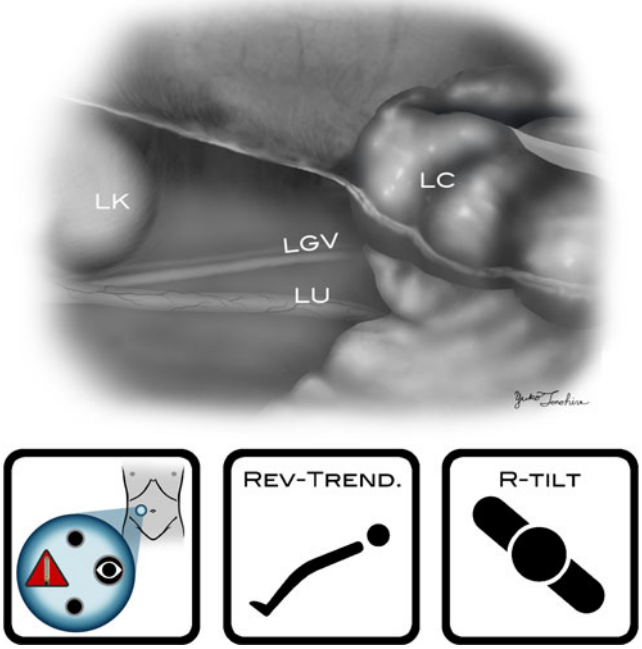

Fig. 4 After complete mobilization of the splenic flexure, the left colon (LC) is retracted toward the pelvis, thus allowing the direct visualization of the left ureter (LU) and left gonadal vessels (LGV). LK: left kidney. In the inserts: the GelPoint is rotated back 180°, with the camera in medial position; the ENSEAL is inserted through the lateral trocar. The table is maintained in reverse Trendelenburg position and right-tilted

Splenic Flexure and Left Colon Dissection

To approach the left colonic angle, the GelPoint is rotated back 180° with the longer arm of the Latin cross and, hence, the camera port is again in the medial position, and the ENSEAL® is moved to the lateral trocar. With the traction applied to the colon toward the midline and the bottom, the splenic flexure is taken sharply. This approach allows for clear visualization of all the structures present in the left upper quadrant, thus allowing for a safe and expeditious splenic flexure mobilization. The descending colon is mobilized by sequentially dividing the lateral attachments and separating Gerota's fascia and Toldt's fascia with blunt dissection. The mobilized colon is progressively retracted toward the pelvis, in the Trendelenburg position, thus allowing the direct visualization of the left ureter (Fig. 4).

Distal Colon Division and Specimen Exteriorization

In order to displace the small bowel and the dissected colon away from the pelvis, the patient is placed in the Trendelenburg position with a slight left lateral tilt. To obtain a more panoramic view of the sigmoid colon, the access device is turned again 180°. A grasper retracts the sigmoid colon upwards. The inferior mesenteric vein and branches of the sigmoid arteries are identified, dissected, and divided with the ENSEAL® close to the colon (Fig. 5). For the final stage of

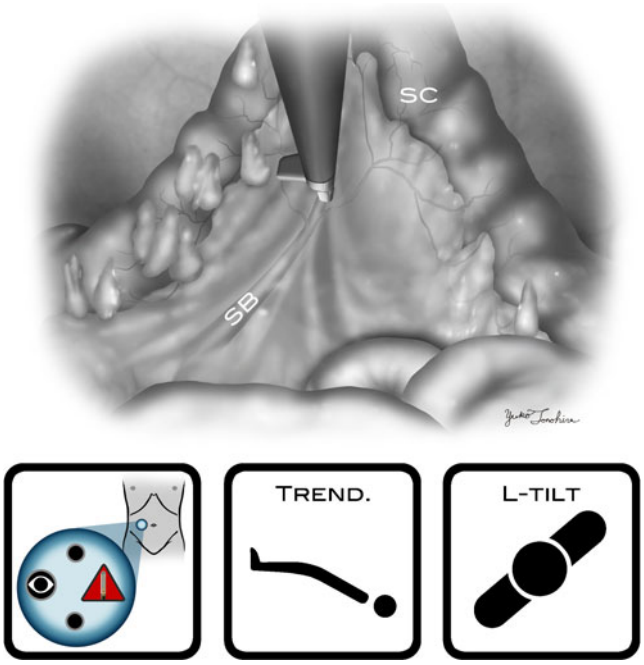

Fig. 5 Identification and division of the sigmoid branches (*SB*), identified retracting the sigmoid colon (*SC*) up in the air. In the *inserts*: the GelPoint is turned 180° one more time, thus having the optical trocar laterally and the ENSEAL medially. The table is now placed in Trendelenburg position and slightly left-tilted

the laparoscopic part of the procedure, we switch to a 5-mm laparoscope that is inserted through the cranial port. The rectosigmoid junction is identified, dissected off the mesentery, and divided with an Endo-GIA stapler.

The peritoneal cavity is inspected for bleeding. The rectosigmoid junction, held with a grasper, is delivered through the single port access, and the entire specimen is exteriorized through the incision. The terminal ileum is divided extracorporeally. The abdominal cavity is copiously irrigated with saline solution until clear. It is our routine practice to place a rectal tube in the rectal stump and secure it in place with a nylon suture. Finally, the ileostomy is matured in the standard Brooke fashion.

Conclusion

In the severely debilitated, malnourished, and immunocompromised patients failing medical management for ulcerative colitis, a minimally invasive approach is intuitively beneficial. In our experience, these patients recover expeditiously and are able to be weaned off ulcerative colitis therapy without delays. We have adopted measures to expedite the surgery such as the removal of the omentum, the transition from a medial to lateral to a lateral to medial approach during the dissection, the use of a single energy source during the entire operation to avoid time-consuming changes and increases in cost, and finally, the liberal use of position shifts to use gravity in our favor. Ten consecutive patients (eight males and two females; mean age, 28±7 years; range, 19–38; BMI, 21.9±2.3) underwent SILS TAC between May and November 2010. The mean operative time was 139±24 min (range, 110–180), with an estimated blood loss of 100±120 ml (range, 20–400). There were no intraoperative complications or conversions to standard laparoscopy or laparotomy. Ostomy output was noted after an average of 1.6±0.7 days (range, 1–3), and solid diet was tolerated on postoperative day 3±0.5 (range, 2–4). The mean length of stay was 5.1±1.3 days (range, 4–7).

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REVIEW ARTICLE

Repair of Parastomal Hernias with Biologic Grafts: A Systematic Review

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Abstract
Background Biologic grafts are increasingly used instead of synthetic mesh for parastomal hernia repair due to concerns of synthetic mesh-related complications. This systematic review was designed to evaluate the use of these collagen-based scaffolds for the repair of parastomal hernias.
Methods Studies were retrieved after searching the electronic databases MEDLINE, EMBASE and Cochrane CENTRAL. The search terms 'paracolostomy', 'paraileostomy', 'parastomal', 'colostomy', 'ileostomy', 'hernia', 'defect', 'closure', 'repair' and 'reconstruction' were used. Selection of studies and assessment of methodological quality were performed with a modified MINORS index. All reports on repair of parastomal hernias using a collagen-based biologic scaffold to reinforce or bridge the defect were included. Outcomes were recurrence rate, mortality and morbidity.
Results Four retrospective studies with a combined enrolment of 57 patients were included. Recurrence occurred in 15.7% (95% confidence interval [CI] 7.8–25.9) of patients and wound-related complications in 26.2% (95% CI 14.7–39.5). No mortality or graft infections were reported.
Conclusions The use of reinforcing or bridging biologic grafts during parastomal hernia repair results in acceptable rates of recurrence and complications. However, given the similar rates of recurrence and complications achieved using synthetic mesh in this scenario, the evidence does not support use of biologic grafts.

Keywords Biologic graft · Allograft · Xenograft · Parastomal hernia

Introduction

Parastomal herniation is a common complication following creation of an ileostomy or colostomy, with observed rates of up to 28% and 48%, respectively.[1] Besides risk of incarceration and stenosis of the bowel, parastomal herniation can cause pain, discomfort and an ill-fitting pouching system that in turn may cause leakage and skin excoriation. Needless to say, body image is adversely affected in patients that might already be experiencing social problems associated with the presence of a stoma.[2] Surgical treatment modalities available are relocation of the stoma and repair of the defect using either direct suture repair, or bridging or reinforcement with prostheses. Relocation of the stoma does not address tissue weakness secondary to systemic risk factors and, just like direct suture repair, often results in high recurrence rates.[3,4] Since the introduction of synthetic mesh to reinforce or bridge the defect, this procedure has been regarded as the best possible care for parastomal herniation, showing lower recurrence rates.[1,5] Its prophylactic use at the time of initial stoma creation is now often propagated to prevent future herniation.[5,6] At the same time, reservations have arisen with respect to the implantation of synthetic mesh in close proximity to bowel and stoma due to risk of erosion and fistula formation.[7] Also, dense adhesions may complicate

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future abdominal surgery.[8] Besides these concerns, there is the universal fear of infection when implanting foreign body material, especially in contaminated fields.

Collagen-based biologic grafts have been produced since the 1980s.[9] These prostheses consist of an acellular collagen matrix that is slowly degraded and replaced by fibro-collagenous tissue of the host. Their properties depend on the species and type of tissue that the material is extracted from, the processing methods (including decellularisation and sterilisation), and whether or not they are intentionally cross-linked. Biologic grafts used for incisional hernia repair are derived from either human dermis, porcine dermis, porcine small intestinal submucosa, or bovine pericardium. During processing, the materials are made functionally acellular to prevent a foreign body response, while still maintaining their extracellular collagenous structure that allows for the host tissue ingrowth. Sterilisation of the materials by ethylene oxide gas or irradiation aims at making the final product pathogen free. Some products receive additional cross-linking of the collagen matrix to control or reduce the enzymatic degradation of the graft. This should give the host more time to deposit fibro-collagenous tissue and remodel the prosthesis into strong native tissue. Due to their bio-compatibility resulting in rapid vascularisation and migration of host (immune) cells, it is thought that biologic prostheses are less prone to infection than synthetic grafts. Moreover, they are soft and pliable which potentially decreases the risk of discomfort and erosion into the bowel. However, given the high financial costs of biologic grafts, proper evidence of more beneficial outcomes or cost savings in the long run are paramount to support their use. This systematic review aims to evaluate the use of these acellular collagen-based scaffolds for the repair of parastomal hernias, focusing on recurrence and complication rates.

Methods

Search Methods for Study Identification

Studies were identified using the electronic databases MEDLINE (including in-process and other non-indexed citations, 1950–present), EMBASE (1980–present) and the Cochrane Central Register of Controlled Trials. Search terms used were: ‘parastomal’, ‘paracolostomy’, ‘para-ileostomy’, ‘stoma’, ‘hernia’, ‘defect’ and ‘repair’. Terms were searched for as free text and where applicable were also mapped to MeSH terms. Full-text articles retrieved for evaluation were scanned for other relevant references. No limits were set on language or publication status. Titles and abstracts were screened for eligibility and full-text articles were retrieved. The last search was performed on 13 September 2010. All reports on repair of parastomal hernias using a acellular collagen-based biologic scaffold as sole material to reinforce or bridge the defect were included. All other types of repair were excluded.

Assessment of Study Quality

All studies selected were subjected to a modified version of the Methodological Index for Non-Randomised Studies (MINORS) tool to evaluate their methodological quality (Table 1). This instrument was constructed and validated

Table 1 Modified Methodological Index of Non-Randomised Studies (MINORS)

Item	Criteria	Option	Score
1	A clearly stated aim	Not reported	0
		Partially reported, no clear aim	1
		Clear aim	2
2	Minimum of 5 included patients	No	0
		Yes	2
3	Inclusion of consecutive patients	Not reported	0
		Patients in a certain time period	1
		Consecutive patients+characteristics	2
4	Type of stoma specified	Not reported	0
		Reported	2
5	Surgical technique reported	Not reported	0
		Incomplete	1
		Reported clearly, appropriate to aim	2
6	Report of end points	Not reported	0
		Recurrences only	1
		Recurrences and postoperative complications	2
		Maximum score:	12

for appraisal of non-randomised trials in surgery.[10] Studies were scored independently by two authors (NJS, RPB). This modified version contains six items with a maximum score of two on each, yielding a maximum index of 12. Studies with a total score less than nine, or no score on item 2, 5 or 6 were excluded from systematic review. Disagreement was resolved by discussion and consensus between authors. Also, the diagnostic modality for the primary outcome was determined for every study.

Data Extraction

The primary outcome was the rate of parastomal hernia recurrence observed, as defined by the respective authors. Study characteristics (year of publication, no. of patients, surgical technique, follow-up), perioperative (30 days) mortality and rates and type of wound-related complications were also noted. Total amount of wound-related complications were calculated by adding up all relevant complications, including only the studies with adequate reporting. Weighted pooled proportions with their respective 95% confidence intervals (CI) following the fixed-effects (inverse variance) model were determined for recurrences and wound-related complications using StatsDirect® statistical software.[11]

Results

A flowchart overview of the search is depicted in Fig. 1. The search strategy yielded 333 titles and abstracts. After screening, 317 records were excluded leaving 16 articles to be retrieved and assessed for eligibility. Six of these were excluded after assessment[12–17] leaving a total of 10 articles that reported on the repair of parastomal hernias with biologic prostheses. After subjecting these to the modified MINORS tool, another six were excluded due to too small sample sizes[18–22] and inadequate reporting on surgical technique.[23] This left four studies to be included in the systematic review.[24–27]

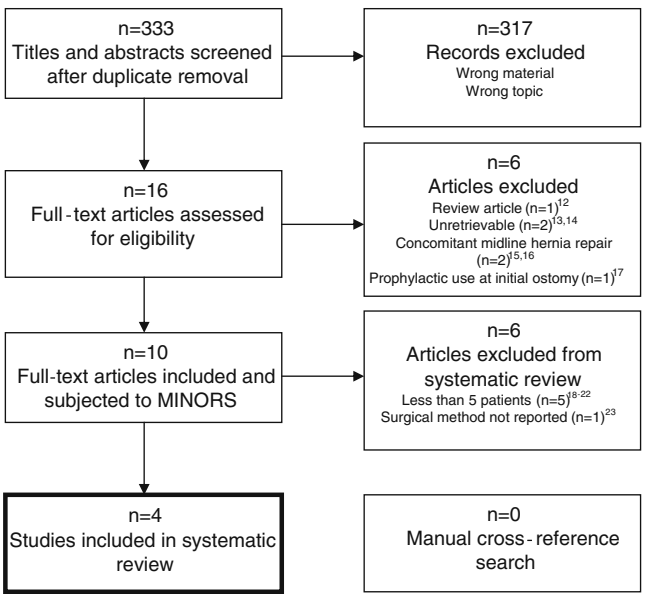

Fig. 1 Flowchart of search strategy

Findings of Systematic Review

All included studies were retrospective with a combined enrolment of 57 patients (range 11–20). The definition of a recurrence was not given by any author. Follow-up ranged from 8.1 to 50.2 months, and was done by clinical examination in three[25–27] and also by CT imaging in one.[26] One study was unclear as to how follow-up was performed.[24] No mortality was reported. Study characteristics and outcomes including weighted pooled rates of recurrence and wound-related complications are shown in Table 2. The weighted pooled proportion of recurrences was 15.7% (95% CI 7.8–25.9; Fig. 2). No cases of infected grafts were reported. Araujo et al. only reported on infection (which was absent) and therefore their data were not included in the calculation of wound-related complications. Various surgical techniques were used, including onlay, inlay, and underlay (pre- and intraperitoneal) placement of the biologic graft. Both open and laparoscopic procedures were performed. Biologic grafts used were products derived from human acellular dermis (Alloderm®), bovine pericardium (Peri-Guard®) and porcine small intestinal submucosa (Surgisis®). Characteristics of the biologic grafts used in the included and excluded studies are given in Table 3.

Studies Excluded From Systematic Review

Six reports on the use of biologic grafts for the repair of parastomal hernias were excluded after subjecting them to the modified MINORS tool, including retrospective studies,[20,23] case reports[19,21] and case series[18,22] (Table 4). Two case reports and two case series described the use of biologic grafts for the repair of parastomal hernia. Greenstein and Aldoroty[19] reported on a patient with a history of ulcerative colitis and four ileostomy revisions that presented with unremitting obstructive symptoms. An incarcerated parastomal hernia confirmed by CT was repaired using cross-linked porcine dermis (Collamend®) in a retromuscular fashion. Patient regained ileostomy function within a few days and when seen at 18 months was pain free with no evidence of graft infection, hernia recurrence, ileostomy malfunction or obstruction. Lo Menzo et al.[21] reported on a patient with a history of abdominoperineal resection for rectal cancer that presented with a three-time

Table 2 Study characteristics and recurrence rates of studies included in systematic review

Reference	Year	No. of patients	MINORS index	Material used	Type of repair	No. of wound complications (%) [b]	Recurrence (%)	Months follow-up (range)
Araujo et al.[24]	2005	13	10	Peri-Guard	Onlay	n/a	1 (7.7)	50.2 (n/a)[a]
Aycock et al.[25]	2007	11	9	Alloderm	Inlay (n=8) and onlay (n=3)	2 (18.2)	3 (27.3)	8.1 (1–21)
Taner et al.[26]	2009	13	9	Alloderm	Under+onlay sandwich	5 (38.5)	2 (15)	9 (4–16)
Ellis[27]	2010	20	12	Surgisis	Intraperitoneal underlay (Sugarbaker)	4 (20.0)	2 (10)	18 (6–38)
Weighted pooled%[c] (95% CI)	–	–	–	–	–	26.2% (14.7–39.5)	15.7% (7.8–25.9)	–

[a] This follow-up is that of a larger group of which these patients were part of

[b] Complications: wound infection (3),[5,26] seroma formation (6),[26,27] incisional separation (2)[26]

[c] Using a fixed-effects (inverse variance) model

recurrent parastomal hernia, for which an expanded polytetrafluoroethylene mesh was used for the last repair using the keyhole technique. The Sugarbaker technique[28] was employed using bovine pericardium (Veritas®). Postoperatively, a seroma developed which resolved spontaneously; and at 17-month follow-up, there was no evidence of recurrence, the patient was pain free and satisfied with cosmetic results. In a case series of three patients, Kish et al.[22] reported on the primary repair of parastomal hernia using human acellular dermis (Alloderm) as onlay reinforcement. Two patients were followed for 6 months and 1 year, respectively, and remained hernia free. One patient presented 8 months later with symptoms of intestinal obstruction treated conservatively. The patient subsequently returned 3 months later with intestinal obstruction and recurrent parastomal hernia that necessitated an operation for relocation of the stoma and repeat hernia repair. Inan et al.[18] reported on two patients, one with a history of proctectomy after severe radiation proctitis presenting with discomfort and obstructive episodes, the other presenting with symptomatic hernia 18 years after abdominoperineal resection. Both were repaired laparoscopically using cross-linked porcine dermis (Permacol®), and at 9 and 3 months postoperatively there was no evidence of recurrence or mesh-related complications.

Two retrospective studies on the use of cross-linked porcine dermis (Permacol) for various types of hernia repair in complex, infected or potentially contaminated settings, included six patients undergoing parastomal hernia repair. Of the total of 133 procedures, Franklin et al.[23] repaired parastomal hernia using intraperitoneal onlay mesh in two patients, showing no recurrences.[20] Follow-up ranged 1–78 months using clinical examination. Loganathan et al.[23] reported on repair of four parastomal hernias, one of which underwent reversal of the colostomy at the time of the hernia repair. Of the other three patients, one that had six

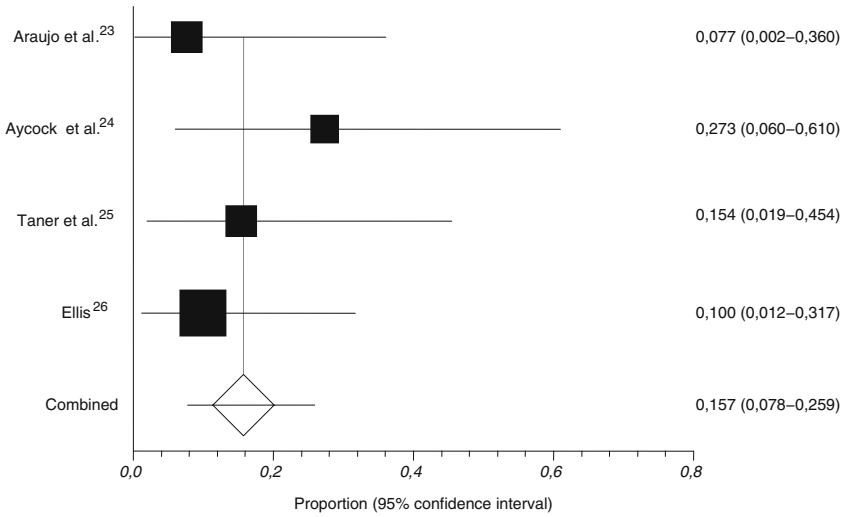

Fig. 2 Weighted pooled proportion (fixed-effects model; Cochran's Q=1.917, p=0.5899) of recurrences after parastomal hernia repair using biologic grafts

Table 3 Characteristics and costs of biologic and synthetic prostheses used for parastomal hernia repair

Material	Source	Additional cross-linking	Preparation	Costs per cm^{2a}
Alloderm	Human dermis	None	Refrigeration, rehydration	$ 35.31
Permacol	Porcine dermis	Yes; HMDI	None	$ 18.97
Surgisis	Porcine SIS	None	Rehydration	$ 20.00
Collamend	Porcine dermis	Yes; EDC	Rehydration	$ 18.88
Peri-guard	Bovine pericardium	Yes; gluteraldehyde	Rehydration	$ 3.91
Veritas	Bovine pericardium	None	None	$ 22.02
	Polypropylene/e-PTFE/Composite	–	None	$ 3.65

[a] Based on sheet sizes sufficient for parastomal hernia repair, excluding account discount. Manufacturers and distributors were contacted directly via telephone

SIS small intestinal submucosa; *HMDI* hexamethylene diisocyanate; *EDC* 1-ethyl-(3-dimethylaminopropyl) carbodiimide hydrochloride; *Alloderm* LifeCell Corp., Branchburg, NJ, USA; *Permacol* Tissue Science Laboratories, Aldershot, UK; *Surgisis* Cook Surgical, Bloomington, IN, USA; *Collamend* Bard Inc., Warwick, RI, USA; *Xenmatrix* Brennen Medical Inc., St. Paul, MN, USA; *Veritas, Peri-Guard* Synovis Surgical Innovations, St. Paul, MN, USA

previous attempts at hernia repair experienced a recurrence. This patient developed an ischaemic end ileostomy which subsequently developed a localised perforation which manifested as a fistula formation. Another patient also developed a fistula. Cross-linked porcine dermis (Permacol) was placed as inlay or onlay. Median follow-up of the complete series was 377 days (range 85–1,905 days) performed by clinical examination.

Discussion

The current systematic review evaluated the use of biologic grafts for parastomal hernia repair, which results in acceptable rates of recurrence, with a pooled rate of 15.7% (95% CI 7.8–25.9). Wound-related complications were reported in 26.2% (95% CI 14.7–39.5). Given the current evidence, biologic grafts do not provide a superior alternative to other surgical options.

In their review on parastomal hernia from 2003, Carne et al.[1] shed some light on the outcomes of different techniques of parastomal hernia repair. In studies using synthetic meshes (intraperitoneal, preperitoneal and fascial onlay), the overall recurrence rate was 6/77 (7.8%). Infection is uncommon and only infrequently requires removal of the mesh. A search of the literature published since reveals reherniation occurring in 62/371 (16.7%) patients.[29–42] As found by Carne et al., complications were low, with mesh infection reported in 15/460 (3%) of the patients. In the current systematic review of parastomal hernia repair using biologic grafts, rates of recurrence ranged from 7.7% to 27.3%, with a weighted pooled average of 15.7% (95% CI 7.8–25.9). Graft infection was zero, and other wound-related complications including wound infection were 26.2% (95% CI 14.7–39.5). Thus, these rates are very similar to those found for synthetic mesh. Notably, even the risk of mesh infection appears to be low when a synthetic graft is implanted. Given the current evidence, it cannot be

Table 4 Study characteristics and recurrence rates of studies excluded from systematic review

Reference	Year	No. of patients	Material used	Type of repair	No. of wound complications (%)[b]	Recurrence (%)	Follow-up (range)
Kish et al.[22]	2005	3	Alloderm	Onlay	n/a	1 (33.3)	(6–12)
Inan[18]	2007	2	Permacol	Laparoscopic (method not specified)	n/a	0 (0)	6 (3–9)
Greenstein & Aldoroty[19]	2008	1	Collamend	Retromuscular/sublay	0 (0)	0 (0)	18
Franklin et al.[20]	2008	2	Surgisis	Intraperitoneal onlay mesh (Laparoscopic)	n/a	0 (0)	n/a
Lo Menzo et al.[21]	2008	1	Veritas	Intraperitoneal (Laparoscopic Sugarbaker)	1 (100)	0 (0)	17
Loganathan et al.[23]	2010	3	Permacol	n/a	2 (66)	1 (33)	12 (3–62)[a]

[a] This follow-up is that of a larger group of which these patients were part of

[b] Complications: seroma formation (1),[21] ischaemic ileostomy and subsequent fistula (1),[23] fistula (1)[23]

concluded that biologic prostheses are more preferable than synthetic mesh to reduce the rates of immediate or long-term complications. Moreover, biologic grafts are very expensive compared to synthetic mesh (Table 3), which further refutes their superiority over synthetic mesh to provide not only effective but also efficient and cost-effective healthcare. With limited financial resources, careful consideration must be taken whilst choosing the types of materials to use.

It is well established that parastomal hernias can occur after great periods of time. Also, on the long run, risk of infection may remain higher for non-absorbable synthetic meshes compared to degradable biologic grafts due to a prolonged presence of foreign body material. Studies with longer follow-up are therefore imperative to yield more reliable rates of recurrence and late complications for both these treatment modalities. The results of this systematic review were troubled by typical issues of potential bias, including the lack of uniformity between studies in definition and reporting of outcomes and patient characteristics.

Given the scarcity of relevant studies, combined with the variety of biologic grafts used, it is impossible to make a direct comparison between the different products or types of material. The same goes for the surgical technique used (i.e. the type of prosthetic placement), which is also of relevance for outcome. With synthetic meshes, average rates of recurrence after sublay mesh (5.7%)[34,39] and intraperitoneal mesh (11.1%)[32,33] are lower than after onlay mesh (22.8%)[29–31] or laparoscopically placed intraperitoneal mesh (16.6%).[35–38,40–42] Onlay placement requires extensive dissection of subcutaneous tissue which predisposes for hematoma and seroma formation and may disrupt skin vascularisation leading to impaired wound healing. Moreover, due to its anatomical position, intra-abdominal pressure may lead to lateral detachment of the graft resulting in its higher recurrence rates. On the other hand, sublay and underlay techniques theoretically benefit from the intra-abdominal pressures which may help to keep the graft in place. Concerning complications, the sublay placement again theoretically seems the most advantageous of the techniques, resulting in the least contact between mesh and bowel.

Besides its use for the repair of parastomal hernia, there has been much debate as to the effectiveness of the prophylactic placement of a reinforcing prosthesis at the time of initial stoma formation. In a recent systematic review of the use of a mesh to prevent parastomal hernia, Tam et al.[6] made a strong case for the use of prophylactic mesh at the time of initial stoma formation, showing an overall recurrence rate of 15.4%, compared to 55.2% in patients who received a conventional stoma. Their meta-analysis performed on three randomised controlled trials yielded similar results. Complications were very low and did not differ between the two groups. To date, only one study can be identified that used a biologic graft for this purpose.[17] Hammond et al. compared the prophylactic use of cross-linked porcine dermis (Permacol) to conventional stoma formation. After a median follow-up of only 6.5 months, the conventional group had a recurrence rate of 33.3%, while the prophylactic group showed no recurrences. No complications were observed. Given the very low rate of complications associated with prophylactic synthetic mesh placement, there is as yet no support for the use of biologic grafts instead of synthetic ones in this surgical scenario.

As mentioned earlier, when studying rates of hernia recurrence, next to an appropriate follow-up a properly defined outcome measure is deemed essential to create uniform and comparable findings. None of the studies in the current review provided a proper definition of a recurrence. Most studies used clinical examination to detect hernias, and one study also used CT imaging in all patients.[26] Here, the two patients that had radiologic evidence of a recurrence continued to be asymptomatic at 385 and 509 days follow-up, respectively, requiring no revision of their repair. Another study, which was excluded from this review due to the prophylactic placement of a biologic graft, also used CT imaging in all patients to determine hernia occurrence.[16] Similarly, the only two occurrences were found on CT scan and were small asymptomatic hernias. If these studies had used only clinical examination, it is conceivable that these asymptomatic patients might not have been found to have a recurrence. Most recently, Gurmu et al. examined the inter-observer reliability of clinical examination of parastomal hernia in three hospitals.[43] This appeared to be low, with kappa values ranging between 0.29 and 0.73. The correlation between CT and patient-reported complaints using a colostomy questionnaire was also low, revealing a kappa of 0.45. Even though the underestimation of rates of (minor) parastomal hernias may well be very common, its clinical relevance in asymptomatic and satisfied patients is only manifest in an increased risk of complications due to the hernia, such as incarceration and stenosis of bowel. It is hard to estimate these risks in patients with asymptomatic or small hernias, but given the marginal amount of recurrences and long-term complications in the studies discussed in this review and in the literature, they do not seem to give cause for concern.

Conflict of interest None of the authors have a conflict of interest or financial tie to disclose.

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REVIEW ARTICLE

The Opioid Component of Delayed Gastrointestinal Recovery After Bowel Resection

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Abstract
Introduction Patients undergoing bowel resection or other major abdominal surgery experience a period of delayed gastrointestinal recovery associated with increased postoperative morbidity and longer hospital length of stay. Symptoms include nausea, vomiting, abdominal distension, bloating, pain, intolerance to solid or liquid food, and inability to pass stool or gas. The exact cause of delayed gastrointestinal recovery is not known, but several factors appear to play a central role, namely the neurogenic, hormonal, and inflammatory responses to surgery and the response to exogenous opioid analgesics and endogenous opioids.
Discussion Stimulation of opioid receptors localized to neurons of the enteric nervous system inhibits coordinated gastrointestinal motility and fluid absorption, thereby contributing to delayed gastrointestinal recovery and its associated symptoms. Given the central role of opioid analgesics in delayed gastrointestinal recovery, a range of opioid-sparing techniques and pharmacologic agents, including opioid receptor antagonists, have been developed to facilitate faster restoration of gastrointestinal function after bowel resection when used as part of a multimodal accelerated care pathway. This review discusses the etiology of opioid-induced gastrointestinal dysfunction as well as clinical approaches that have been evaluated in controlled clinical trials to reduce the opioid component of delayed gastrointestinal recovery.

Keywords Gastrointestinal motility · Drug effects · Mu-opioid receptor antagonists · Perioperative care

Pathogenesis of Delayed Gastrointestinal Recovery After Bowel Resection

Patients undergoing bowel resection (BR) or other major abdominal surgeries experience delayed gastrointestinal (GI) recovery manifested by a temporary interruption of coordinated bowel motility, ineffective intestinal transit, and inability to tolerate oral intake.[1–3] Delayed GI recovery occurs universally after BR; however, the severity and duration can vary significantly, and identifying patients who are at greater risk for serious occurrences remains a challenge. Clinical signs include nausea and vomiting, abdominal distension, bloating, pain, intolerance of solid food, and inability to pass stool or gas (Table 1).[2] These symptoms typically resolve 2 to 4 days after surgery but may last a week or longer, resulting in longer hospital length of stay (LOS) and increased utilization and cost of healthcare resources.[2] Delayed GI recovery may also lead to increased postoperative pain, delayed wound healing, and increased risk of nosocomial complications such as infection, venous thromboembolism, or hyponutrition.[2]

Considerable interest has been expressed in understanding the underlying pathophysiologic mechanisms associated with delayed GI recovery. The exact causes of delayed GI recovery have yet to be elucidated; however, it has become increasingly clear that at least four interrelated mechanisms

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Table 1 Clinical signs and effects of delayed GI recovery[2]

Increased incidence of nausea and vomiting
Delayed resumption of oral feeding
Delayed absorption of orally administered medications
Increased postoperative pain
Delayed wound healing
Delayed postoperative ambulation
Increased risk of postoperative complications:
Atelectasis
Aspiration pneumonia
Deep venous thrombosis
Pulmonary embolism
Bacterial translocation and sepsis
Nosocomial infections
Increased hospital length of stay
Increased patient discomfort and decreased satisfaction
Increased healthcare cost

and physiologic responses are involved. These include inflammatory and hormonal responses to BR, neurogenic reflexes, and the pharmacologic effects of opioids.[4,5] Understanding the roles of these pathways in the pathogenesis of delayed GI recovery has led to the development of novel methodologies and treatments that are being evaluated to either prevent delayed GI recovery or to accelerate the return of normal GI function. An earlier return of GI function offers clear benefits by improving outcomes, reducing postoperative morbidity, facilitating early hospital discharge, improving patient satisfaction, improving quality of care, and reducing overall costs.[2,6,7]

Pathophysiology of Delayed GI Recovery

Normal bowel function is a complex, coordinated interaction between GI motility, mucosal transport, and defecation reflexes.[8,9] Peristaltic motion of the GI tract is under independent and integrated control of the enteric nervous system (ENS), which is structurally and functionally similar to the central nervous system (CNS). The ENS controls multiple effectors involved in normal physiologic GI function, including smooth muscle contractile activity, glandular secretions, and blood flow. The ENS can act independently but also communicates extrinsically with the CNS through afferent and efferent pathways via the parasympathetic vagus and sacral nerves and sympathetic nerve fibers of the prevertebral ganglia. Synaptically connected sensory neurons, interneurons, and motor neurons originating in the myenteric and submucosal plexuses of the ENS innervate the entire length of the GI tract and coordinate an adaptive response to different digestive states. Excitatory and inhibitory stimulation of enteric neurons is mediated by many of the same signaling molecules found in the CNS, including acetylcholine, serotonin, opioids, and nitric oxide (NO). Therefore, agonistic or antagonistic reagents that interact with neurally localized receptors to elicit physiologic responses in the CNS may also interact with receptors localized to neurons of the ENS, although the consequences of these interactions may be quite different.

The pathophysiology of delayed GI recovery is multifactorial and complex (Fig. 1).[4,5] After surgery, electrical activity mediated by the ENS is disorganized, and propulsion lacks normal coordination. Surgical incision and manipulation of the gut elicit a multiphasic physiologic response resulting in impaired GI neuromuscular function and dysmotility. At least two distinct phases of impaired GI function have been identified, which can be distinguished by their different timing and underlying pathophysiology. In the early neurogenic phase, nociceptive stimulation activates adrenergic and vagally mediated neural reflexes resulting in increased sympathetic muscle tone and inhibition of normal bowel motility. This phase is triggered during surgery and ends soon after the incision is closed. Therefore, the underlying mechanisms responsible for early neurogenic GI dysmotility are not thought to be responsible for the sustained lack of GI function observed in the postoperative period.

About 3 to 4 h after surgery, a late phase of GI dysmotility is triggered, mediated by localized and systemic inflammatory responses to surgical insult.[5] Leukocytes residing in the bowel wall (most likely macrophages) are activated to secrete a variety of proinflammatory cytokines, which activate gut-resident leukocytes, triggering an influx of circulating lymphocytes and increased production of NO and cyclooxygenase-2 (COX-2). These mediators act directly on gut tissue smooth muscle cells to impair neuromuscular function and inhibit normal GI contractile activity. The key role played by leukocyte extravasation in this response was demonstrated in experimental model systems of GI inflammation by blocking expression of intracellular adhesion molecule-1, which prevented infiltration of circulating lymphocytes and reduced inhibition of GI muscle contractile activity.[10,11] Local inflammation is also triggered when mast cells localized to the site of surgery release vasoactive substances in response to intestinal handling that increase mucosal permeability and allow luminal bacterial or proinflammatory bacterial components such as lipopolysaccharides to enter the lymphatic system.[12–14] These substances also act distantly to activate spinal afferents, leading to a more generalized state of GI dysmotility that more closely resembles what is typically observed in the postoperative period.[5]

In addition to neural and inflammatory responses, perioperative stimulation of peripheral opioid receptors localized to enteric neurons contributes significantly to the

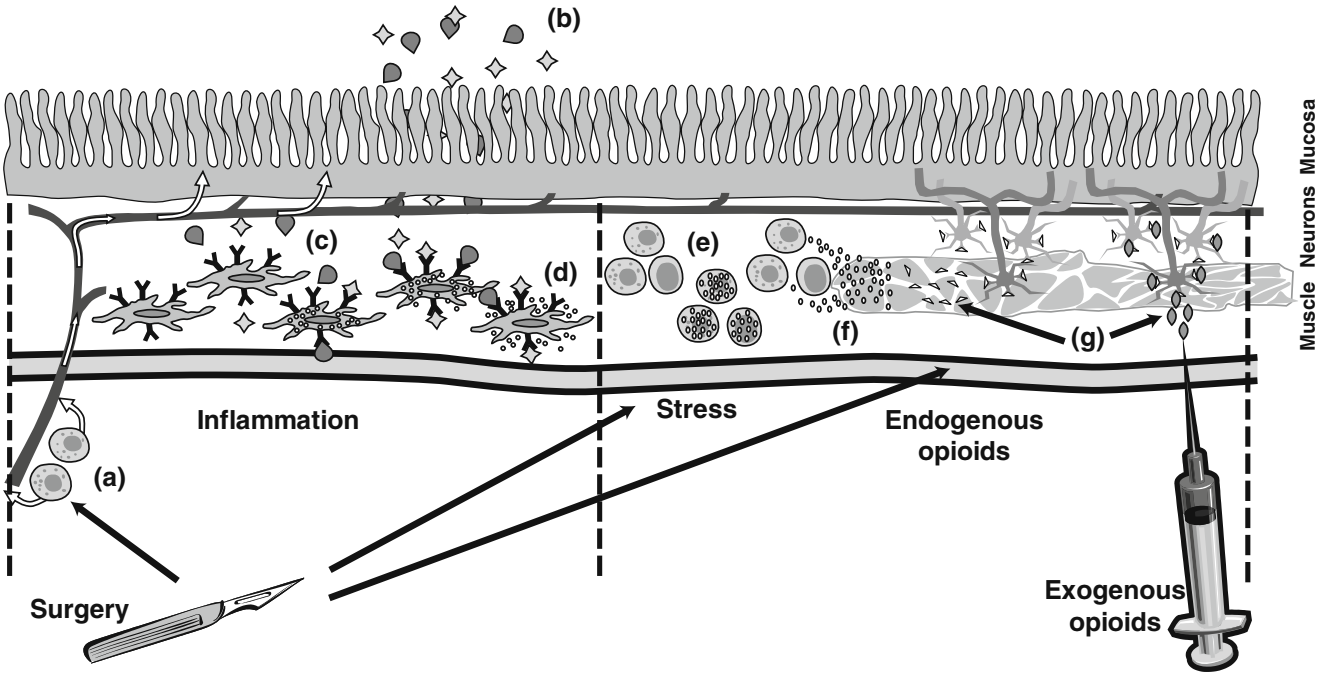

Fig. 1 Multifactorial pathophysiology of delayed GI recovery.[5] Surgical incision and manipulation of the intestines activates inflammation, stress responses, and endogenous opioids. Mast cells (**a**) release vasoactive substances that diffuse into blood vessels, thereby increasing mucosal permeability and allowing entrance of luminal bacteria and LPS (**b**) into the intestinal wall. Recognition of bacterial components by resident macrophages (**c**) leads to macrophage activation, stimulating the release of chemokines and inflammatory cytokines (**d**) that attract leukocytes (**e**) to the intestinal muscularis. Inflammatory cells secret large amounts of nitric oxide and prostaglandins (**f**), which impair smooth muscle contraction. Endogenous and exogenous opioids (**g**) disrupt GI transit and motility through interaction with mu-opioid receptors localized to neurons innervating GI smooth muscle. *GI* gastrointestinal, *LPS* lipopolysaccharide

pathophysiology of delayed GI recovery. Opioid receptors in the CNS are well documented to be involved in analgesia when activated by endogenous and exogenous opioid receptor agonists. However, in the ENS, stimulation of opioid receptors contributes significantly to postoperative GI dysmotility. The remainder of this review will focus on the opioid component of delayed GI recovery in more detail.

The Opioid Component of Delayed GI Recovery

Opioids have been used for centuries as treatment for dysentery and diarrhea, as well as for management of perioperative and chronic pain. However, the adverse effect of opioid analgesia in causing GI dysfunction is also well established (Table 2).[15] Opioids used for pain management during and after surgery exert their adverse effects on GI motility independent of route of administration. Thus, intramuscular opioid administration, systemic opioid administration with intravenous (IV) patient-controlled anesthesia (PCA), or opioid epidurals can all lead to varying degrees of opioid-induced GI dysmotility.[9] Additional undesirable consequences of opioid analgesia include respiratory suppression, impaired absorption of oral drugs, anorexia, urinary retention or incontinence, decreased quality of life, and possible increased likelihood of cancer recurrence.[16–18] The undesirable consequences of opioid analgesia persist throughout the course of treatment and are often relieved only by reduction or termination of opioid medication. However, opioids are a mainstay of perioper-

Table 2 Effects of opioids on the GI tract[15]

Pharmacologic action	Clinical effect
Decreased	
Gastric motility	Decreased appetite, increased gastroesophageal reflux
Pyloric tone	Nausea and vomiting
Enzymatic secretion	Delayed digestion; hard, dry stool
Inhibition of small and large bowel propulsion	Delayed absorption of medication, straining, incomplete evacuation, bloating, abdominal distension, constipation
Increased	
Fluid and electrolyte absorption	Hard, dry stools
Nonpropulsive segmental contractions	Spasms, abdominal cramps, pain
Anal sphincter tone	Incomplete evacuation

ative pain management and are likely to remain so in light of current guidelines for pain management that emphasize the consequences of inadequate pain relief and promote better pain control.[19,20]

The clinical effects of opioid analgesics are similar to those of endogenous opioids and are mediated through stimulation of membrane-associated opioid receptors that localize predominantly to central and peripheral nerves and to GI and vascular smooth muscle cells.[8,21] Three major classes of opioid receptors, each with multiple subtype variants, have been described: the delta-, kappa-, and mu-opioid receptors, which selectively interact with different opioids to mediate a broad spectrum of physiologic responses.[22] A fourth receptor type, the nociception receptor, bears structural and functional homology to opioid receptors but has very low affinity for commonly used opioid agonists or antagonists.[23] Delta-opioid receptors localize mainly to the CNS but are also detected in the myenteric plexus of the ENS, whereas kappa-opioid receptors are widely distributed in the CNS and ENS. Both delta and kappa receptors contribute to analgesia, and kappa receptors likewise are involved in bowel dysfunction and sedation. However, the bulk of the benefits (analgesia) and adverse effects (bowel dysfunction) of opioid analgesics are mediated through interactions with mu-opioid receptors. The mu receptor class is composed of three subtypes, of which two are differentially expressed in the brain (mu_1 receptor) and in the GI tract and spinal cord (mu_2 receptor) but have similar ligand affinity.[9] In contrast, the mu_3-receptor subtype has little affinity for the well-characterized endogenous mu receptor ligands but is potently activated by morphine.[24]

The endogenous ligands for opioid receptors include enkephalins and dynorphins, which are the preferred ligands of delta and kappa receptors, respectively, and endomorphins and beta-endorphin, which are the preferred ligands for mu_1 and mu_2 receptors, respectively.[21] Endomorphins exhibit the highest receptor specificity, which is several thousand-fold higher for mu receptors than for delta and kappa receptors.[25] Endogenous opioids and their cognate receptors are expressed by both central and peripheral nerves. In the GI tract, enkephalins primarily localize to myenteric neurons projecting to the circular muscle and submucosal plexus, and dynorphins primarily localize to submucosal and myenteric neurons and fibers originating from the celiac ganglion.[9,22] On the other hand, endorphin expression in the GI tract appears to be limited to endocrine cells, and endomorphin expression has not been detected in the GI tract.

Most endogenous opioids are small polypeptides derived from the proteolytic cleavage of larger precursor proteins. An endogenous nonpeptide morphine that is produced in response to stress and that interacts with mu_3 receptors has also been described and is found in several human tissues, such as adrenal glands, liver, and neutrophils.[26] Exogenous opioids are structurally distinct, nonpeptide ligands that are either naturally occurring (e.g., the opiate alkaloids morphine, codeine, and thebaine), semi-synthetic derivatives of natural opiates (e.g., hydrocodone and oxycodone), or fully synthetic (e.g., fentanyl and methadone).[27]

In the CNS, opioid receptors localize to the cerebral cortex, striatum, and hippocampus of the brain. The effects mediated by stimulation of opioid receptors in the CNS include not only analgesia but also euphoria, sedation, and respiratory depression. In the GI tract, opioid receptors are localized to neurons of the myenteric and submucosal plexus and endocrine cells of the intestinal mucosa that control motility and secretion. Activation of opioid receptors inhibits release of excitatory neurotransmitters, including acetylcholine, at both pre- and post-synaptic sites. Excitation of neurons innervating the intestinal smooth muscle results in distension and peristaltic contractions. Likewise, blockade of inhibitory neural signals decreases release of NO from motor neurons, resulting in increased muscle tone and decreased propulsive GI transit. Concurrently, opioid-induced suppression of excitatory secretomotor neurons reduces secretion and liquidity of contents in the intestinal lumen. Other effects of opioids on the GI tract include decreased pyloric tone and gastric emptying, as well as increased anal sphincter tone.

In addition to the untoward effects of opioids on GI motility, anti-inflammatory effects have been attributed to opioids that may also exacerbate return of normal GI function. Increased plasma concentrations of endogenous morphine are observed in the first 5 days after surgery and have been proposed to help downregulate the postoperative inflammatory response via interaction with mu_3-opioid receptors found on granulocytes and monocytes.[26] Consistent with this, administration of morphine increases plasma levels of corticotropin-releasing hormone, adrenocorticotropic hormone, and glucocorticoids, which are all known to suppress the immune system. Moreover, patients receiving higher doses of opioids have a significantly higher risk for postoperative infections.[28,29] In a recent prospective clinical trial, expression of endogenous morphine was significantly higher ($P<0.001$) in the first 48 h after surgical procedures associated with greater inflammation (open BR) compared with surgical procedures associated with less inflammation (laparoscopic BR). Levels of endogenous morphine correlated significantly with increased mean time to GI recovery and longer time to hospital discharge observed with open BR.[30] Therefore, GI recovery after surgical procedures associated with more extensive inflammation may be prolonged because of a greater anti-inflammatory counterresponse that includes increased expression of endogenous morphine.

Mitigating the Effect of Opioids

Acceleration of postoperative GI recovery is central to decreasing postoperative morbidity and hospital LOS. Implementation of multimodal accelerated care pathways is a key component of this process. Multimodal pathways have incorporated a variety of perioperative modalities to minimize the physiologic response to BR, including minimally invasive surgery, no preoperative bowel preparation, fluid management, early feeding and ambulation, opioid-sparing anesthesia and analgesia, and pharmacologic agents to mitigate opioid-related side effects. Many of these elements have been evaluated singly in prospective clinical trials, but the additive or synergistic effects of a comprehensive multimodal care pathway have not been formally addressed in many well-controlled, randomized, clinical trials (RCTs). Nevertheless, techniques or agents that reduce opioid exposure and opioid-related side effects are central to proposed multimodal accelerated care pathways, highlighting the fundamental role of opioids in the etiology of delayed GI recovery (Table 3).

Non-opioid Analgesics (NSAIDs, COX-2 Inhibitors, Acetaminophen, Gabapentin)

Multimodal analgesia is a strategy based on the use of multiple agents from different pharmacologic drug classes. These agents have different modes of action and may act additively or synergistically to manage pain, thereby reducing opioid consumption and decreasing opioid-related side effects. Examples include non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors (coxibs), and other common analgesics. Although these agents show considerable potential to reduce opioid exposure, they also have their own unique side effect profiles, and the benefit–risk ratio of adding each agent to a multimodal analgesia protocol must be considered at the level of the individual patient. There is a limited number of prospective, well-controlled trials evaluating the opioid-sparing effects and side effect profiles associated with multimodal analgesia. Future clinical trials are also needed to evaluate drug-specific side effects associated with these agents when given in combination.

A meta-analysis of placebo-controlled RCTs comparing NSAIDs or coxibs added to morphine after surgery demonstrated that morphine consumption, and nausea and vomiting were both reduced by approximately 30% in patients receiving either an NSAID or coxib.[31] Likewise, in a randomized, double-blind study, pre- and postoperative administration of valdecoxib reduced morphine consumption and significantly reduced time to first bowel movement (BM) and toleration of solid food compared with placebo in patients undergoing open BR.[32] However, no difference was observed in postoperative nausea in patients who received valdecoxib. Traditional NSAIDs, including flurbiprofen and ketorolac, have also been evaluated in prospective clinical trials of patients undergoing open BR.[33,34] Flurbiprofen reduced pain scores and decreased time to first flatus and BM but did not reduce nausea and vomiting compared with placebo when combined with thoracic epidural anesthesia and patient-controlled epidural analgesia (PCEA). Likewise, ketorolac added to IV PCA

Table 3 Mitigating the effects of opioids after BR

Technique	Positive clinical effect[a]							
	GI	BM	Flatus	VAS	Morph	NV	Food	LOS
Non-opioid analgesia								
Ketorolac and NSAIDs	–	Y	Y	Y	Y	–	–	Y
COX-2 inhibitors	–	Y	Y	Y	Y	–	Y	Y
Gabapentin	–	–	–	Y	Y	Y	–	–
Acetaminophen	–	–	–	Y	Y	–	–	–
Non-systemic analgesia								
Epidural analgesia	–	–	–	Y	Y	–	–	–
Epidural bupivacaine	Y	Y	–	Y	Y	–	–	–
Epidural with local anesthetic	–	Y	Y	Y	Y	–	–	–
PAM-OR antagonist								
Alvimopan	Y	Y	Y	–	–	Y	Y	Y
Ghrelin agonist								
TZP-101	Y	Y	–	–	–	–	Y	Y
Prokinetic agent								
Bisacodyl	–	Y	Y	–	–	–	–	–
Minimally invasive surgery	Y	Y	–	Y	Y	–	Y	Y

[a] Positive clinical effect on the specified measure in 1 or more well-controlled, randomized clinical trial

BM first bowel movement, *BR* bowel resection, *COX-2* cyclooxygenase type 2, *flatus* first flatus, *food* toleration of oral diet, *GI* time to gastrointestinal recovery after BR as measured by a composite endpoint, *LOS* hospital length of stay, *Morph* morphine or supplementary analgesic consumption, *NSAIDs* non-steroidal anti-inflammatory drugs, *NV* nausea and vomiting, *PAM-OR* peripherally acting mu-opioid receptor, *VAS* visual analog scale pain score, *Y* yes

morphine reduced morphine consumption and time to first BM compared with IV morphine alone. However, ketorolac provided no significant benefit in terms of visual analog scale (VAS) pain scores or nausea and vomiting.

Acetaminophen has not been assessed in a well-controlled, prospective study in patients undergoing BR; however, in placebo- or active-controlled trials of gynecologic surgery, it was found to be equivalent to IV ketorolac in reducing postoperative pain scores.[35] Moreover, a meta-analysis of RCTs comparing acetaminophen plus PCA morphine to PCA morphine alone after major surgery reported that acetaminophen induced a significant morphine-sparing effect. It had no effect, however, on postoperative morphine-related adverse events or patient satisfaction.[36]

Gabapentin, a calcium channel modulator used to treat chronic neuropathic pain, has not been rigorously evaluated in patients undergoing BR; however, a systemic review of RCTs comparing gabapentin to inactive controls in patients undergoing various surgeries concluded that gabapentin is not associated with a significant reduction in nausea and vomiting.[37] In a RCT conducted in patients undergoing hysterectomy, gabapentin reduced morphine consumption by up to 32% and reduced pain scores.[38] These data suggest that RCTs to evaluate the opioid-sparing effects of gabapentin in patients undergoing BR are warranted.

Epidural and Thoracic Epidural Analgesia

Thoracic epidural is more appropriate than lumbar epidural for both anesthesia and analgesia in patients undergoing BR. Sympathetic input to the GI tract occurs at the fifth thoracic spinal level and below. Therefore, mid-thoracic epidurals block sympathetic nerves to the GI tract, providing analgesia, improving splanchnic blood flow, and decreasing GI muscle tone. Although PCEA has demonstrated better pain control than traditional IV-PCA, variability in study protocols makes evaluation and comparison across studies difficult.[39] Moreover, technical or medical issues may limit the use of epidurals at some institutions or in patients who cannot tolerate or refuse to receive the procedure. In a systematic review comparing continuous epidural analgesia with IV-PCA after intra-abdominal surgery, epidural analgesia provided superior pain relief for up to 72 h after surgery.[40] A second systematic review demonstrated that adding local anesthetic to the epidural provided similar pain control as epidural opioid analgesia alone and reduced time to return of GI function.[41]

In prospective, randomized trials in patients undergoing open BR, epidural local anesthetic significantly reduced pain scores for 2 to 3 days compared with standard protocols using general anesthesia and/or IV-PCA morphine.[42,43] However, there was no difference in nausea and vomiting reported in these studies, and the benefits in terms of GI recovery and hospital LOS were inconsistent. In another prospective, randomized study, pain scores were lower and time to GI recovery was shorter for patients who received epidural analgesia, but frequency of nausea and vomiting and nasogastric tube (NGT) insertion and hospital LOS were similar between patients who received epidural analgesia and patients who received general analgesia alone.[44] Likewise, a meta-analysis of clinical trials in patients undergoing BR found lower pain scores in patients who received epidural analgesia compared with systemic opioids, but no significant difference in nausea and vomiting or hospital LOS.[45] Epidural analgesics have opioid-sparing effects, can improve pain scores, and can decrease time to GI recovery compared with systemic opioid analgesia; however, they are less effective at reducing morphine side effects such as nausea and vomiting or reducing hospital LOS.

The benefit of epidural anesthesia is similar in patients who undergo laparoscopic surgery. In a prospective, randomized study of patients undergoing laparoscopic BR who received either thoracic epidural anesthesia or morphine IV-PCA postoperatively, thoracic epidural anesthesia was associated with lower postoperative pain scores compared with patients receiving morphine IV-PCA. However, incidence of morphine-related side effects, time to return of bowel function, and hospital LOS were similar between groups in this study.[46] Taken together, the data on opioid-sparing pain management protocols suggest that they provide benefit in terms of shorter time to GI recovery and lower pain scores, but these benefits do not necessarily translate into shorter hospital LOS.

Pharmacologic Options

Opioid-sparing elements of multimodal accelerated care pathways have potential to decrease the time to GI recovery and to reduce postoperative pain. However, implementation of opioid-sparing techniques must be balanced against evolving standards for pain management that currently stress the importance of reducing patients' pain scores to levels that, in some patients, may only be achievable with opioid analgesia. In these patients, techniques that minimize or reduce opioid-related side effects without sacrificing opioid analgesia will be of great value.

Pharmacologic interventions to minimize opioid-related side effects while maintaining opioid-based analgesia have been under continuous development; however, only two drugs have thus far been approved by the FDA to mitigate the adverse effects of opioids. These agents, methylnaltrexone and alvimopan, are peripherally acting mu-opioid receptor (PAM-OR) antagonists that have high specificity for and block activity at mu-opioid receptors outside of the CNS.[15] After systemic IV (methylnaltrexone) or oral

(alvimopan) administration, the large, polar, molecular structures of the PAM-OR antagonists impede transit across the blood–brain barrier, thus limiting effects in the CNS.[15] Specific antagonism of peripheral mu-opioid receptors reduces opioid-related adverse effects in the periphery (e.g., GI dysmotility, nausea, and vomiting) without compromising opioid-based analgesia in the CNS.[15] Both methylnaltrexone and alvimopan have been studied in large, randomized, phase 3 clinical trials, which served as registration trials for their approval by the US FDA.[47–51] However, only alvimopan is approved for the acceleration of GI recovery after partial small or large BR with primary anastomosis, whereas methylnaltrexone is approved for treatment of opioid-induced constipation in palliative care patients.

The efficacy and safety of alvimopan were assessed in four randomized, placebo-controlled, phase 3, clinical trials conducted in North America.[47,48,50,51] In each study, a standardized multimodal accelerated care pathway was used in both placebo and alvimopan arms. A multimodal pathway plus alvimopan accelerated mean time to GI recovery as assessed by a composite endpoint, GI-2 (the later of the time to first BM or the time to first toleration of solid food, defined as no nausea or vomiting within 4 h of eating at least half of provided food), by 13 to 26 h ($P<0.05$ for all trials) and mean time to hospital discharge order written by 13 to 21 h ($P<0.05$ for three trials) compared with multimodal pathway plus placebo in patients undergoing laparotomy who received postoperative opioid-based PCA.[52] Pain scores and daily opioid use were similar for alvimopan and placebo, and alvimopan significantly reduced the rate of nausea and vomiting compared with placebo ($P<0.001$).[53] Alvimopan was not evaluated in patients undergoing laparoscopic BR in these trials; however, in a recent prospective/retrospective combination study, alvimopan significantly reduced mean (95% confidence interval (CI)) hospital LOS in patients undergoing either open BR (−1.2 days (95% CI=−2.6, –0.2 days)) or laparoscopic BR (−1.1 days (95% CI=−1.7, –0.4 days)) compared with historical control patients.[54] In contrast to the alvimopan phase 3 studies, these results were achieved without use of a standardized multimodal accelerated care pathway, suggesting that alvimopan may provide benefit in a variety of care practices.

A group of compounds referred to as ghrelin agonists are also under development to mitigate opioid-related side effects. Ghrelin is a peptide hormone that binds to growth hormone secretagogue receptors (GHSR-1a), which mediate multiple GI functions, including motility and gastric emptying. A small-molecule ghrelin agonist, TZP-101, was evaluated in a randomized, phase 2 dose-ranging study of patients undergoing open BR who were scheduled for multimodal postoperative care and were expected to receive opioid-based IV-PCA.[55] TZP-101 administered IV significantly accelerated time to first BM by 22 h ($P=0.03$) and time to readiness for hospital discharge by 20 h ($P=0.03$) at the most efficacious dose (480 μg/kg) compared with placebo. TZP-101 also accelerated the time to GI-2 by 21 and 23 h ($P\leq0.04$) at the low efficacious dose (80 μg/kg) and most efficacious dose, respectively, compared with placebo. Opioid usage did not alter the efficacy of TZP-101, and the reported rate of nausea and vomiting was lower in patients receiving TZP-101 compared with placebo. Further studies at the most efficacious dose are needed to fully assess the efficacy of TZP-101. A second ghrelin agonist, ipamorelin, has shown promise to accelerate GI recovery in animal models[56] and is currently being evaluated in clinical trials.

Additional agents under development to accelerate GI recovery after BR include mosapride, a selective serotonin 5-hydroxytryptamine 4-receptor agonist; TU-100 (daikenchuto), a herbal extract originally described in ancient China; and escin, a horse chestnut extract widely used in China for postoperative edema.[57–59] Mosapride has been reported to promote bowel motility and gastric emptying by increasing release of acetylcholine, and it demonstrated promising effectiveness in a small RCT in patients undergoing laparoscopic BR.[58] However, there are no additional, ongoing, or planned trials to evaluate mosapride in this indication. Likewise, evaluation of escin for improving GI recovery after colorectal surgery in a small, placebo-controlled RCT conducted in China yielded positive results based on passage of first flatus and BM, but the development status of this compound is not clear.[59] Additionally, a recently completed, randomized, dose–response trial of TU-100 in healthy volunteers reported no overall treatment effects on gastric emptying and frequency of BM and non-significant differences in colonic filling compared with placebo.[57] It is not clear how the use of opioids may affect the activity of any of these compounds, and additional clinical studies are clearly needed.

Promotility Agents

Promotility agents (i.e., laxatives) are commonly given to patients undergoing colorectal surgery and opioid-based analgesia who experience delayed GI recovery. However, very few well-controlled, randomized trials have been conducted to evaluate this common practice. The effects of bisacodyl on return of GI function, opioid consumption, and frequency of opioid-related side effects in patients undergoing colorectal surgery have been evaluated in a single RCT. Bisacodyl significantly decreased time to first BM ($P=0.001$) compared with placebo but provided no benefit on VAS pain scores, opioid consumption, nausea and vomiting, or hospital LOS.[60] These results suggest that bisacodyl may accelerate GI recovery after BR; however, it

would still need to be combined with other agents to effectively mitigate other morphine-related side effects or to reduce opioid consumption.

Incorporation of Opioid-Sparing Techniques into Clinical Practice

Reduction of opioid-related side effects is an important goal of multimodal accelerated care pathways; however, individual components must be integrated with other pathway modalities to maximize patient recovery and reduce morbidity and mortality. Despite compelling data for the advantages of multimodal pathways, there has been slow adoption of new therapies and techniques into standard clinical practice. A recent survey of general and colorectal surgeons found that only 30% of surgeons worked at a hospital with an established multimodal accelerated care pathway for elective BR that included accelerated GI recovery components.[61] The same survey found that the most common practice among surgeons was preoperative bowel preparation, which was used by 89% of the surgeons who participated in the survey[61] despite strong evidence that it provides no benefit to the patient.[62] This example illustrates the major disparity that exists between protocols developed by evidence-based medicine and standard clinical practice. The sheer number of pathway modalities that are reported in the literature, coupled with inconsistent or inconclusive results in many studies and limited data on the implementation of a full multimodal approach, complicates the decision to implement specific modalities. A successful approach may be to use protocol elements and expertise that are already in place as a foundation for development of improved multimodal care and to gain consensus of the entire perioperative team before making modifications to established protocols.[63] Common practices such as routine thromboprophylaxis, prophylactic antibiotics, avoidance of hypothermia, early ambulation, early oral intake, and NGT removal may provide a solid foundation for subsequent introduction of multimodal analgesic control and minimally invasive surgery. A multidisciplinary team approach is vital to successful implementation of new protocols.

Conclusions

Opioids are an essential component of postoperative pain control. However, both endogenous and exogenous opioids alter bowel function, contributing to delayed postoperative GI recovery. Opioids may also play a role in postoperative inflammatory or immunosuppressive responses and exacerbate the physiologic response to surgery. The available evidence suggests that opioid-sparing anesthesia and analgesia have some positive effects on delayed GI recovery and postoperative pain and that pharmacologic agents that antagonize peripheral opioid receptors are effective at accelerating GI recovery as part of a multimodal accelerated care pathway. Ideally, all appropriate patients undergoing BR should be managed with a combination of minimally invasive surgical techniques, epidural and opioid-sparing analgesia, and PAM-OR antagonists. Well-controlled, robust clinical trials are needed to evaluate whether this is an optimal approach to minimize opioid-related side effects. The available evidence suggests that these techniques may reduce postoperative GI dysfunction. In cases where one or more of these techniques are not appropriate for the patient, having additional options to consider may allow for more effective individualized perioperative care. Novel agents are under development that may also broaden the effective choices available to the surgical team. Institution of evidence-based modalities to multimodal accelerated care pathways can be a challenging endeavor and requires cooperation and participation of all members of the perioperative care team.

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GI IMAGE

Pancreatoduodenal Junction: Review of Anatomy and Pathologic Conditions

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Abstract
Introduction The pancreatoduodenal junction is a small anatomic area where pathologic processes involving the distal bile duct, duodenum, pancreatic head, ampulla de Vater, and retroperitoneum converge. Differential diagnosis includes a spectrum of entities that ranges from anatomical variants to malignancies.
Purpose The aim of this paper was to review the anatomy and different pathologic conditions, whether tumoral, inflammatory, or congenital in origin, in this specific area that involves the pancreatic head, duodenum, duodenal ampulla, distal pancreatobiliary tract junction, and retroperitoneum.
Methods Computed tomography (CT) and magnetic resonance (MR) help us to identify specific radiologic signs that allow to divide the pancreatic-duodenal junction abnormalities into three cathegories: (1) normal variants and congenital anomalies (pancreas divisum, santorinicele, annular pancreas,duodenal duplication cyst, choledocal cyst,...); (2) acquired non-tumoral: traumatic, iatrogenic, inflammatory (duodenal hematoma, duodenal iatrogenic perforation, groove pancreatitis, gastroduodenal artery pseudoaneurysm,...); (3) tumoral (pancreatic head adenocarcinoma, periampullary tumors, neuroendocrine pancreatic tumors, duodenal adenocarcinoma,...). The images illustrate morphologic aspects of these entities.
Results and Conclusions CT and MR are the most appropiate imaging modalities to evaluate pancreatoduodenal junction. Knowing the imaging features is crucial to reach the right diagnosis and treatment of the different entities that involve this anatomic area.

Keywords Pancreatoduodenal groove · Pancreas CT · Pancreas MR · Duodenum CT · Duodenum MR

The pancreatoduodenal groove is a potential space bordered by the head of the pancreas, duodenum, and common bile duct. This is a very small anatomical area where pathologic processes that involve the pancreatic head, duodenum, distal pancreatobiliary tract, duodenal papilla, and retroperitoneum converge. Differential diagnosis includes a spectrum of entities that ranges from anatomical variants to malignancies.

Computed tomography (CT), magnetic resonance (MR) imaging have revolutionized the diagnostic imaging. The complex anatomic relationships of a variety of structures in this small area of the upper abdomen have given rise to diagnostic challenges in which a variety of benign and neoplastic processes often mimic primary neoplasia of the involved structures.

It is important for the radiologist and surgeons to be familiar with the wide spectrum of anatomic variants and pathologic entities that can involve this anatomic area in order to initiate the appropriate lesion-specific work-up and treatment, and avoid unnecessary tests or procedures.

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The aim of this paper was to review by means of CT and MR the different pathologic conditions, whether tumoral, inflammatory, or congenital, that affect this area

Anatomic Landmarks

This anatomic area is bordered medially by the pancreatic head. The second portion of the duodenum forms the lateral border. The descending duodenal serosa surface is intimately related to the pancreatic head covering the pancreatoduodenal groove. The posterior border is formed by the third portion of the duodenum or the inferior vena cava, and the anterosuperior border by the first duodenal portion or duodenal bulb[1]

The pancreatic head contains distal bile duct and the main and accessory pancreatic ducts. In the medial duodenal wall, major and minor papillae are located.

Along the pancreatoduodenal groove runs the superior pancreatoduodenal artery, a branch of the gastroduodenal artery that anastomoses with the inferior pancreatoduodenal artery, a branch of superior mesenteric artery, establishing an anatomic and radiologic landmark between pancreatic head and duodenum (Fig. 1). There are small lymph nodes in the groove generally not depicted on imaging.

CT and MR help us to identify specific radiologic signs that allow to divide the pancreatoduodenal junction abnormalities into three categories:

1. Normal variants and congenital anomalies (páncreas divisum, santorinicele, annular pancreas, duodenal duplication cyst, choledochal cyst,...)
2. Acquired non-tumoral: traumatic, iatrogenic, inflammatory (duodenal hematoma, duodenal iatrogenic perforation, groove pancreatitis, pancreatoduodenal artery pseudoaneurysm,...)
3. Tumoral (pancreatic head adenocarcinoma, periampullary tumors, neuroendocrine pancreatic tumors, duodenal adenocarcinoma,...)

1. Normal variants and congenital anomalies.

   – Pancreas divisum: is the most frequent variant of pancreatic ductal configuration and occurs in 2–7% of general population. In this condition, at the seventh/eighth week of gestation, dorsal and ventral pancreatic ducts fail to fuse. Dorsal duct drains directly in the minor papilla while ventral duct drains in the major papilla. The majority of patients are asymptomatic but a subset of patients has either unexplained abdominal pain or episodes of acute pancreatitis. A relative obstruction to the flow of pancreatic fluid at the level of an inadequately patent or stenosed minor papilla has been hypothesized to result in an increase in intraductal pressure with consequent pancreatitis. On imaging, CT or MR cholangiopancreatography (MRCP) demonstrate separate pancreatic ducts draining to the region of the minor and major ampulla[2] (Fig. 2a, b).
   – Duodenal duplication: duplication cyst can be localized in any part of gastrointestinal tract, and the duodenum is not an uncommon site. Although most of them are not communicated with the lumen, it can occur. The typical symptoms, if present, are related with obstruction or complication as distension, infection, volvulus, or intussusception. At ultrasonography, there is an anechoic or hypoechoic structure, uni- or multilocular. On CT scan, it is seen as an area of low density with an enhancing wall[3] (Fig. 3a–d).
   – Santorinicele: in a pancreas divisum setting, santorinicele represents a cystic dilatation of the distal dorsal duct, just proximal to the minor papilla (analogous to ureteroceles or choledochoceles). It is the result of relative obstruction and weakness of the distal ductal wall. It is a suggested cause of relative stenosis of the minor papilla resulting in high intraductal pressure, responsible for recurrent episodes of acute pancreatitis

     Dynamic MRCP of the pancreatic duct can be performed after secretin stimulation. This technique improves depiction of pancreatic ducts and may be effective in diagnosing the presence of santorinicele in patients who have pancreas divisum and unexplained recurrent episodes of acute pancreatitis and who might benefit from endoscopic treatment (Fig. 4).[4]
   – Annular pancreas: is the second most common congenital pancreatic anomaly and results in pancreatic tissue encircling, partially or completely, the second portion of the duodenum (Fig. 5). MR cholangiopancreatography delineates the pancreatic duct encircling the duodenum (Fig. 6).

     The presentation in adults differs from that in children. Congenital anomalies and duodenal obstruction are the predominant features in children, and pancreatitis is the main presentation in adults.

     The radiologist is often the first to make the diagnosis of this entity.[5]
   – Choledochocele: is a rare abnormality consisting of cystic or diverticular dilatation of the terminal intramural portion of the common bile duct (Fig. 7). It is classified as choledochal cyst type III in Todani's classification and represents 1.4–5% of choledochal cysts. Choledochocele can be further subdivided into three subtypes: type IIIa

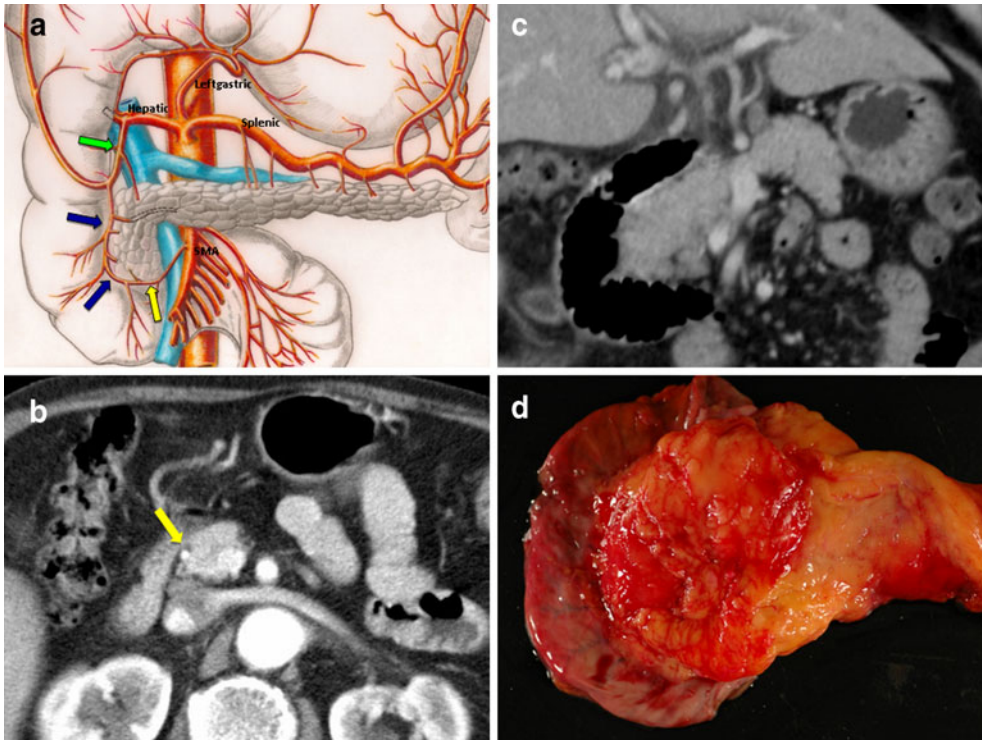

Fig. 1 Vascularization of the pancreatoduodenal area. **a** On the *left* schematic drawing, shown is the gastroduodenal artery (*green arrow*) which supplies blood directly to the pylorus (distal part of the stomach) and proximal part of the duodenum, and indirectly to the pancreas via the superior pancreaticoduodenal artery (*purple arrows*) that establishes an anatomic landmark between pancreatic head and second portion of the duodenum. The inferior pancreaticoduodenal artery (*yellow arrow*) arises from the superior mesenteric artery (AMS) and establishes an anatomic landmark between pancreatic uncinate process and third portion of the duodenum. **b** On the right axial CT image, seen is the level of the second portion of the duodenum showing the superior pancreaticoduodenal artery (*red arrow*) as a landmark between pancreatic head and duodenum. **c**, **d** Coronal MPR and gross specimen (courtesy FJ. Sancho, MD) located in pancreatoduodenal area showing the relationship between the pancreatic head and the second duodenal portion

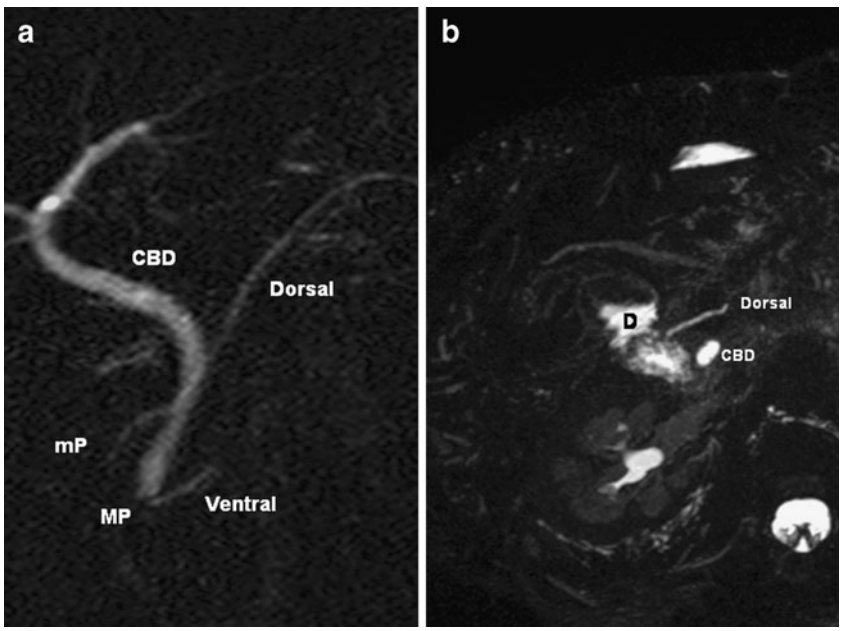

Fig. 2 Pancreas divisum. **a** 2D MRCP showing a complete pancreas divisum. Dorsal duct drains independently into the minor papilla (mP) whereas the ventral duct drains jointly with the common bile duct (CBD) into the major papilla (MP). **b** Axial T2 WI depicts the anterior crossing in the axial plane of the dorsal duct and its independent draining into the minor papilla

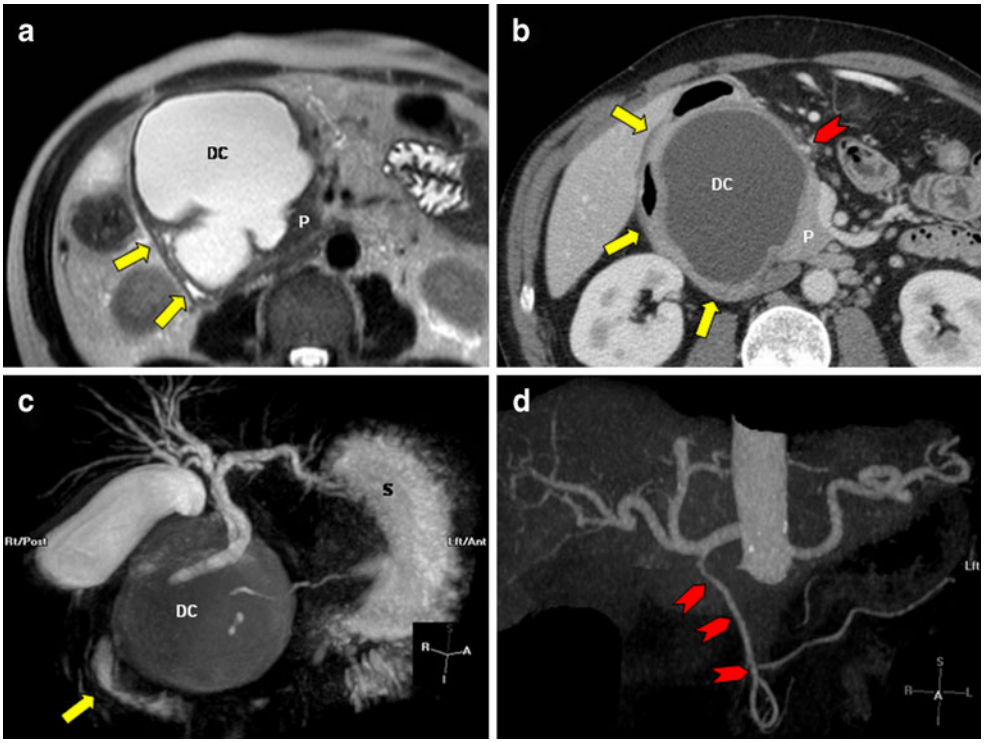

Fig. 3 Duodenal duplication cyst. **a** Axial T2 WI showing duodenal duplication cyst (DC) bordered by the second and third duodenal portions (*yellow arrows*) and medially by pancreatic head (*P*). Thick-walled, well-defined cystic lesions in pancreatoduodenal groove not communicated with duodenal lumen. **b** Axial contrast-enhanced CT at the same level in (**a**). The gastroduodenal artery (*red arrow*) is displaced medially indicating non-pancreatic origin of the lesion. **c** MIP 3D MRCP reformation depicts the laterally displaced second and third duodenal portions (*yellow arrow*). **d** MIP 3D arterial CT showing the medial displacement of the gastroduodenal artery. It represents an indirect sign of non-pancreatic or duodenal origin of the lesion

represents the choledochocele in the intraluminal duodenum and contains the terminal pancreatic and common bile duct as a common channel; type IIIb contains separate ductal structures with an intraluminal cyst, and type IIIc shows a cyst completely contained within the intramural portion of the duodenum.[6]

Some authors have proposed that choledochoceles are congenital in origin while others suggest abnormal biliary motility could be a contributing factor in the pathogenesis of choledochoceles.

Complications of biliary duct cysts include recurrent pancreatitis, pancreatic necrosis, cholangitis, primary cyst stones, and cholangiocarcinoma (2.5%).[7]

2. Acquired non-tumoral: can be further divided into traumatic, iatrogenic, and inflammatory.
   - Duodenal diverticulum: it is the most common acquired alteration of the duodenum. It more commonly arises in the periampullary region along

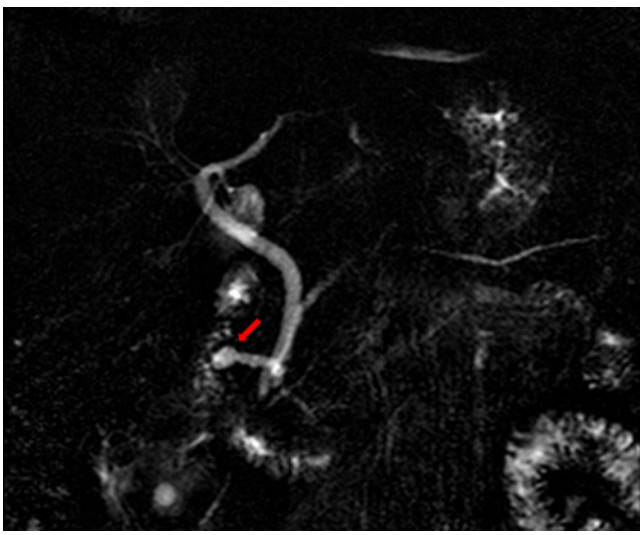

Fig. 4 Pancreas divisum and associated santorinicele. Secretin-stimulated MR-pancreatography helps to depict small cystic dilatation (*arrow*) of the terminal intramural portion of the main pancreatic dorsal duct in a pancreas divisum setting; it is the same case in Fig. 2

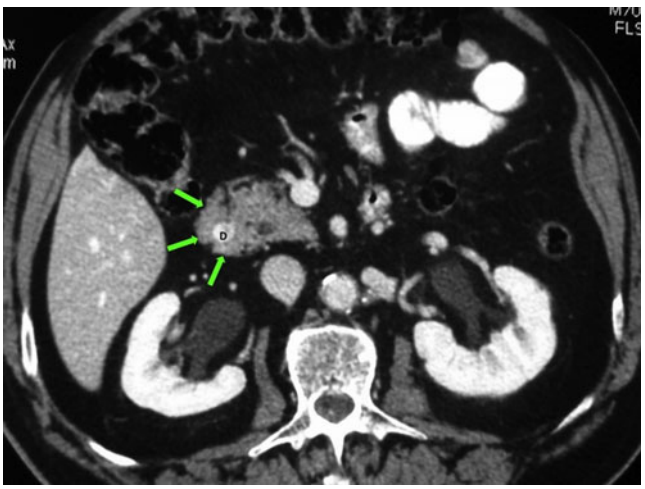

Fig. 5 Annular pancreas. CT image showing pancreatic tissue (*green arrows*) encircling the second portion of the duodenum (*D*)

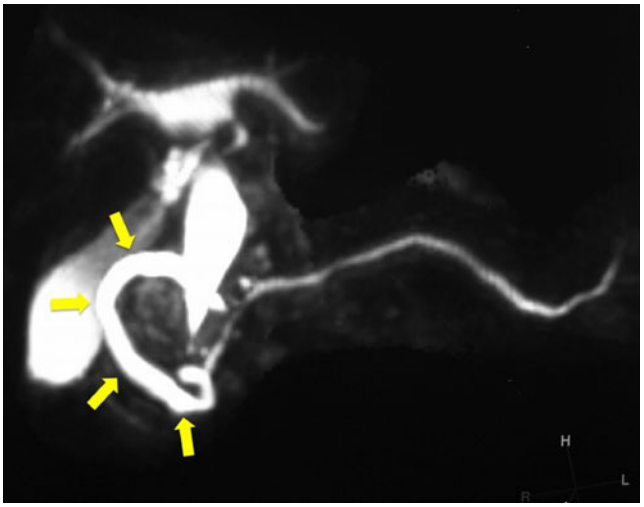

Fig. 6 Annular pancreas. MRCP of an annular pancreas where the ventral duct encircles the second portion of the duodenum for almost 360°. There is a mild dilatation of the ventral duct revealing its obstructive component and the cause of repeated episodes of acute pancreatitis. Choledochal cyst type Ic is present additionally

the medial aspect of the second and third portions of the duodenum. Usually asymptomatic, it can become impacted with debris leading to duodenal diverticulitis and even perforation (Fig. 8) or hemorrhage.[1]

When filled with fluid, it may mimic a cystic neoplasm, abscess, or pseudocyst. The finding of small amounts of gas or oral contrast in the diverticulum clarifies the diagnosis. Intradiverticular drainage of the main bile duct can occur (Fig. 9) and may cause biliary dilatation or preclude a successful endoscopic therapy.[8]

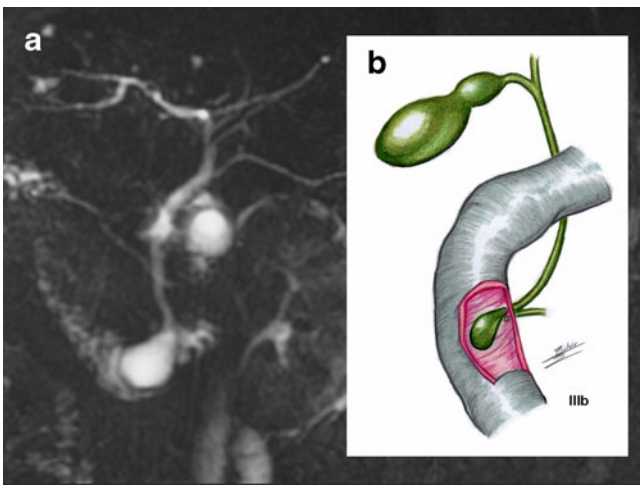

Fig. 7 Choledochocele. **a** MRCP showing the cystic dilatation of the terminal intramural portion of the common bile duct. **b** scheme showing intraluminal choledochocele with separate openings for CBD and pancreatic duct (IIIb)[37]

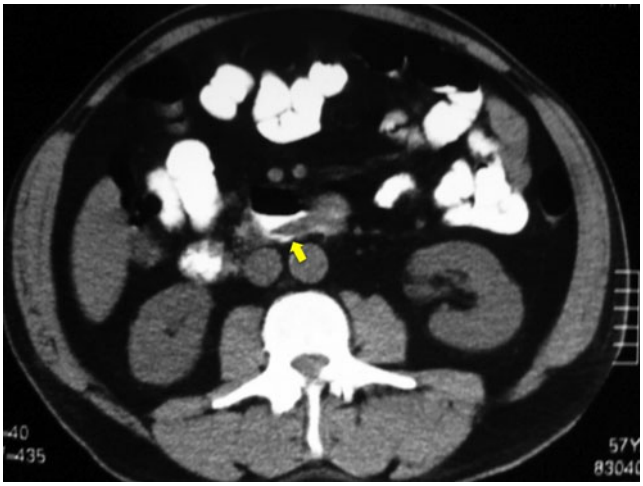

Fig. 8 Duodenal diverticulum rupture. Unenhanced CT scan showing a ruptured diverticulum of the third portion of the duodenum. Oral contrast is out of the duodenal lumen outlining the outer wall of the duodenum, spreading into the retroperitoneum

- Duodenal hematoma: is a rare abdominal injury most commonly seen in children after blunt abdominal trauma, sometimes minor (handlebar trauma, road traffic injury, and sports trauma). Bleeding disorders, Henoch–Schönlein purpura, anticoagulation therapy, alcoholism, pancreatitis, tumors, duodenal ulcers, and local or iatrogenic factors account for the remaining 30% of the cases.[9]

  Duodenal hematoma is a well-recognized manifestation of child abuse.[10]

  The duodenum is crushed against the vertebral body causing contusion or transection that can generate intramural bleeding and hematoma. This hematoma can increase and gradually obstruct the lumen (Fig. 10). Anatomic factors, such as duodenal retroperitoneal fixation, the rich submucosal and subserosal vascular plexus, and a weak muscular abdominal wall, are all contributory to the development of duodenal intramural hematomas.[11]
- Pancreatoduodenal artery pseudoaneurysm: is an uncommon but important complication associated with chronic pancreatitis. Pseudoaneurysm develops because of the action of pancreatic enzymes over the arterial walls. Lesions originate from the erosion of an artery inside a pancreatic pseudocyst by enzymes, mainly elastases, released from the pancreas.

  The most common affected artery by pseudoaneurysm is the splenic artery. Next in frequency are gastroduodenal and pancreatodudenal arteries, followed by left gastric artery, although any local artery can be involved (Fig. 11).[12–14]

  The pancreatoduodenal artery runs along the pancreatoduodenal groove, establishing an anatomic and radiologic landmark between pancreatic

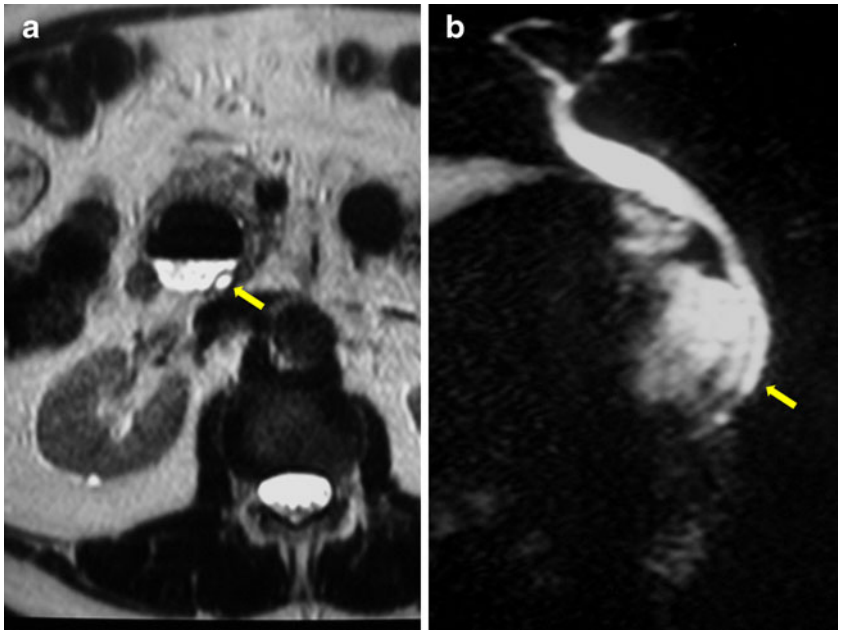

Fig. 9 Intradiverticular papilla. **a** MRCP showing intradiverticular drainage of the main bile duct (*arrow*) in **b** duodenal diverticulapresent a major source of failure for endoscopic retrograde cholangiopancreatography (ERCP) if the common bile duct drains directly into a periampullary diverticulum, obscuring the orifice of the ampulla of Vater. In rare cases, a duodenal diverticulum may become obstructed, resulting in associated duodenal diverticulitis

head and duodenum. On CT imaging, it is seen as an enhanced rounded mass that arises at the pancreatoduodenal groove, rarely exceeding 5 cm in diameter, and usually presenting thin wall calcifications and mural thrombosis. Pseudoaneurysms are often fully asymptomatic, unless they rupture and bleed. About 50% of pseudoaneurysms eventually rupture with major hemorrhage into the retroperitoneum, peritoneal cavity, or intestinal lumen.[15]

– Acute pancreatitis*:* inflammation and fluid collections can be located in duodenopancreatic junction, in the course of acute pancreatitis Serial studies showing changes in fluid collections can help to differentiate acute pancreatitis from groove pancreatitis.[1]
– Groove pancreatitis: is an uncommon type of focal chronic pancreatitis affecting the groove between the head of the pancreas, the duodenum, and the common bile duct (Fig. 12). Patients affected by GP are relatively young men with a history of alcohol abuse in the majority of cases.[16] The clinical setting is similar to other chronic pancreatitis, but recurrent vomiting due to progressive duodenal stenosis represents its main clinical feature.[17]

The pathogenesis of groove pancreatitis remains controversial. Several factors may be related,

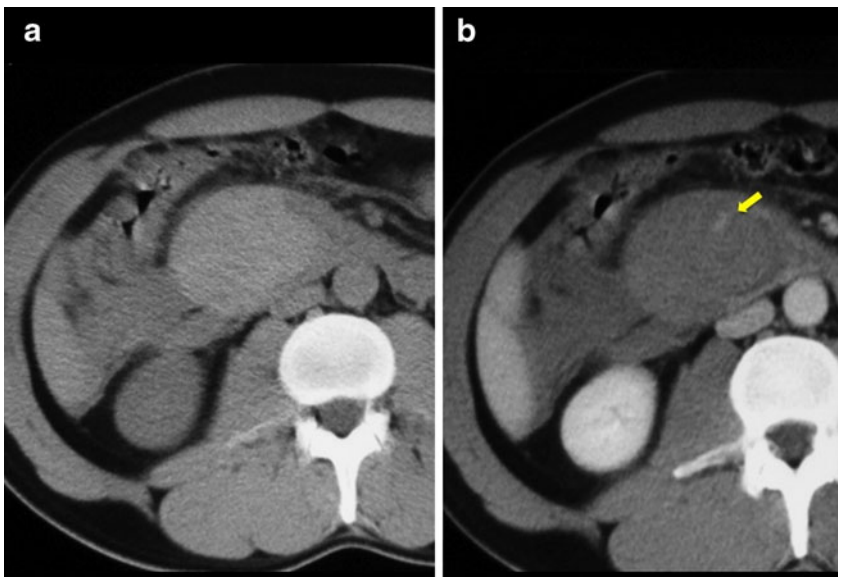

Fig. 10 Duodenal hematoma. **a** Large duodenal hematoma. After an endoscopic procedure to sclerose a duodenal peptic ulcer, a hyperdense intramural mass is seen. On unenhanced CT, it occupies the second portion of the duodenum. **b** After intravenous contrast administration, a small point of active bleeding can be seen (*arrow*) (courtesy J Palmer, MD)

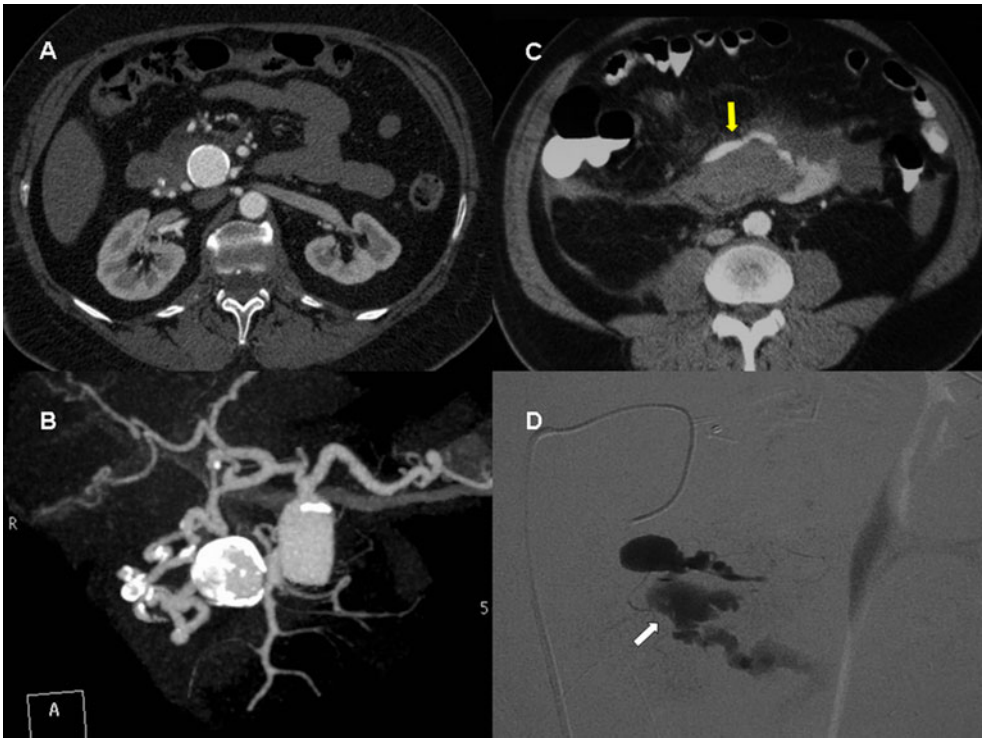

Fig. 11 Gastroduodenal artery pseudoaneurysm rupture. **a**, **b** An enhancing pancreaticoduodenal pseudoaneurysm with mural calcifications in an axial enhanced CT and 3D reconstruction. **c**, **d**. Enhanced CT scan showing a point of active bleeding (*yellow arrow*) from gastroduodenal artery. IV Contrast pools in the left retroperitoneum (*white arrow*)

including previous diseases of the biliary system, peptic ulcers, gastric resections, duodenal wall or pancreatic head cysts, and pancreatic head heterotopia in the duodenum (Fig. 13). Chronic inflammation of the duodenum with scar tissue in the wall leads to fibrosis and stenosis. Cystic changes are frequently encountered according to most accepted theories; they represent cystic dystrophy of a heterotopic pancreas tissue in the duodenal wall.[18]

Two forms of the disease can be recognized, the pure and the segmental one.[19] The pure form

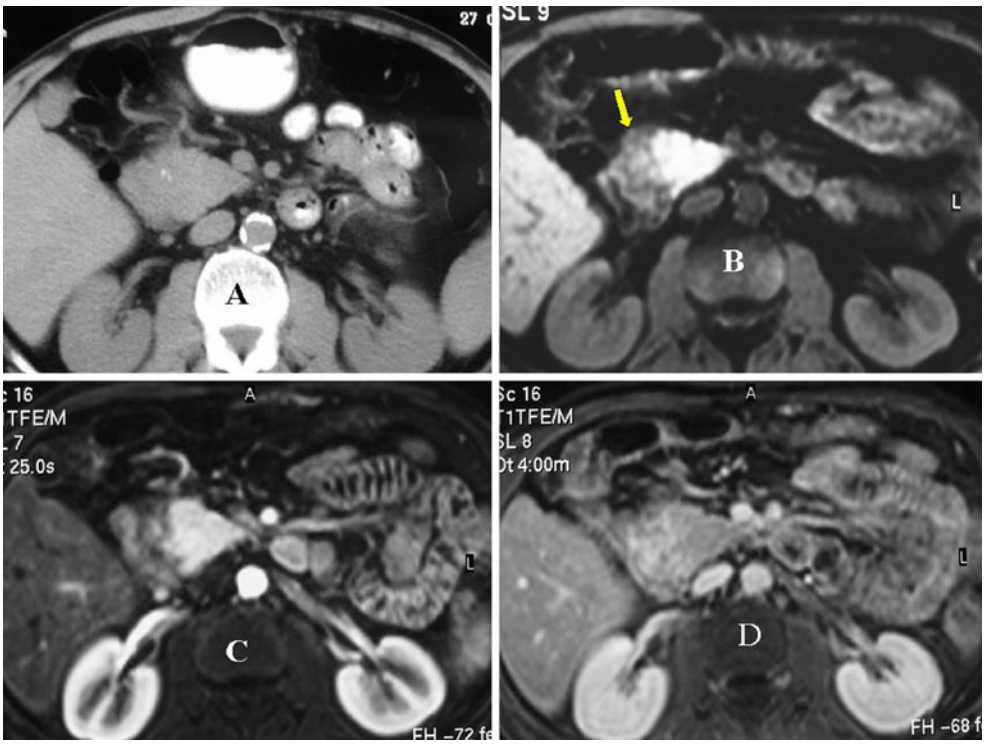

Fig. 12 Groove pancreatitis. **a** Unenhanced CT scan showing mass-like occupation of the pancreaticoduodenal groove. Punctate calcification can be seen. **b** T1WI at the same level clearly depicts the hypointense band (*arrow*) between pancreatic head and the second portion of the duodenum. **c** Arterial phase dynamic Gd-MR shows hypovasculatiry of the T1WI hypointense area. **d** Delayed phase dynamic Gd-MR depicts delayed enhancement of the pancreatitic fibrotic area, characteristic of fibrous tissue

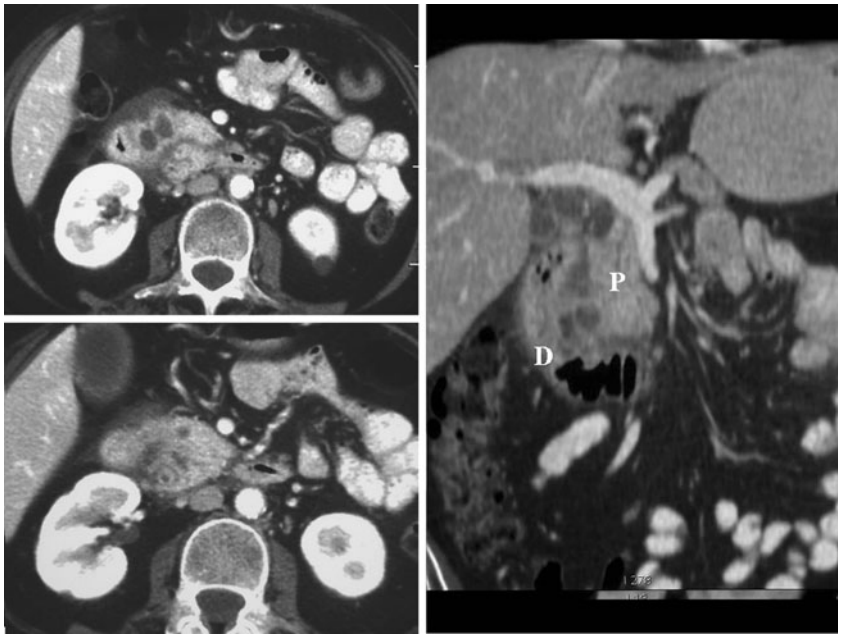

Fig. 13 Groove pancreatitis. On the *left*, two axial enhanced CT scans showing fat stranding around pancreaticoduodenal area, mass-like occupation of the pancreaticoduodenal groove, duodenal wall thickening, and the presence of small cysts. According to the most accepted theories, they represent cystic dystrophy of a heterotopic pancreas in the duodenal wall. On the *right*, enhanced CT coronal reformation depicts the cystic and hypodense band between the pancreas (*P*) and the second portion of the duodenum (*D*)

affects the groove only, while the pancreatic parenchyma is preserved. The segmental form predominantly involves the head of the pancreas in proximity to duodenal wall.[20]

On CT, a hypodense mass-like lesion can be identified between the pancreatic head and the duodenum. The peripancreatic vessels used to be preserved, even in extensive disease. In the segmental form, the main pancreatic duct may be mildly dilated in the pancreatic body and tail, while, in the pure form of the disease, it usually appears normal.[17]

On MR, the mass is hypointense to pancreatic parenchyma on T1-weighted images and can be hypo-, iso-, or slightly hyperintense on T2-weighted images. Delayed images show heterogeneous enhancement due to the fibrous tissue.[17] Main differential diagnosis of groove pancreatitis is the groove pancreatic adenocarcinoma of the pancreas which is often very difficult to differentiate due to the lack of specific discriminating imaging features. It is crucial to arrive at a right diagnosis since groove pancreatitis is usually managed with conservative medical treatment while pancreatic adenocarcinoma is treated with surgery in a radical curative attempt.

As mentioned above, in groove pancreatitis, peripancreatic vessels used to be preserved while

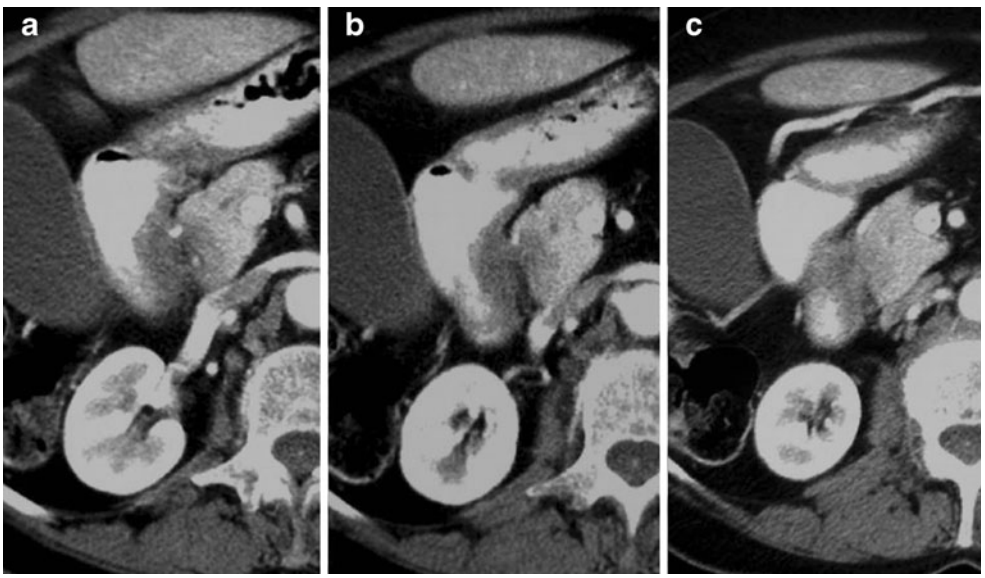

Fig. 14 Groove pancreatic adenocarcinoma. **a**–**c** Descending contiguous enhanced CT scans showing a pancreatic adenocarcinoma arising in the pancreaticoduodenal groove as a solid infiltrating mass that encases gastroduodenal artery. No cystic lesions are seen within the mass. Although endoscopic biopsy of the duodenum ulcers are required, the findings on CT make pancreatic adenocarcinoma the more likely diagnosis

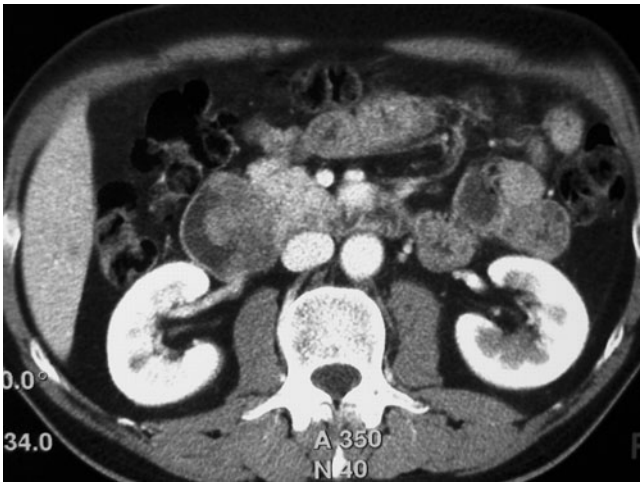

Fig. 15 Duodenal adenocarcinoma. CT scan shows a solid intraluminal soft-tissue mass in the medial wall of the second duodenal portion with transmural invasion into the pancreatic head

pancreatic carcinoma is expected to invade along large peripancreatic vessels.[16]

As reported by Yu et al. on MR cholangiopancreatography, the stenosed intrapancreatic portion of the bile duct in patients with segmental form of groove pancreatitis used to be longer and smoother, in contrast to the abrupt and irregular ductal stenosis seen in patients with pancreatic carcinoma.[1]

To consider groove pancreatitis in the differential diagnosis of pancreatic carcinoma is fundamental for an appropriate management. Differentiating both entities is difficult based only on radiologic features.[21] MRCP can be helped by endoscopic retrograde cholangiopancreatography (ERCP). Both may show the smooth and regular stenosis of the common bile duct, characteristic of groove pancreatitis or the irregular ductal stenosis typically seen in pancreatic carcinoma.[22] Unfortunately, despite the advances in technology and the exhaustive use of imaging techniques, surgical resection is required to reach the diagnosis.

Although discussing the surgical technique is beyond the aim of this article, the Whipple technique is the most frequently performed. The information provided by CT scans about vascular and invasion of surrounding structures, and by endoscopic ultrasonography and ERCP in case of extrahepatic biliary obstruction,[23] is crucial in order to plan a pancreatoduodenectomy.

3. Acquired tumoral:

   – Groove pancreatic adenocarcinoma: pancreatic ductal head adenocarcinoma arises from the epithelium of the main pancreatic duct or a side branch and sometimes can present as a pancreatic exophitic mass arising in groove area; the main pancreatic duct can be spared from invasion. In these cases, it cannot be reliably differentiated from groove pancreatitis by means of CT and MR.[17] The findings of cystic lesions within the mass, lack of gastroduodenal artery invasion, and thickened duodenal wall with scarring and stenosis of duodenal lumen are more common in groove pancreatitis. On the contrary, vascular encasement suggests malignancy (Fig. 14). Main pancreatic

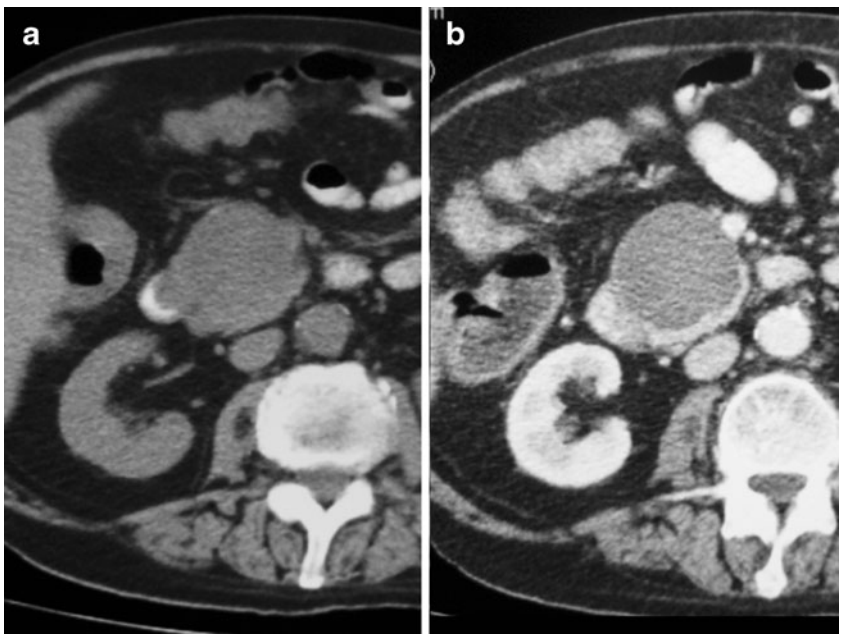

Fig. 16 Duodenal gastrointestinal stromal tumor. **a** Unenhanced CT scan shows a large tumoral mass, predominantly extraluminal, arising in the medial wall of the second portion of the duodenum. **b** Contrast-enhanced CT scan shows well-defined mass with peripheral high attenuating rim and central areas of low attenuation

duct dilatation can occur in both cases. Biopsy of duodenal mucosa invaded is the clue to reach the diagnosis. Groove pancreatitis should be considered in the differential diagnosis of pancreatic head tumor.[24]

– Duodenal adenocarcinomas: is the most common primary malignant neoplasm, with the 50–70% of small bowel adenocarcinomas arising from duodenum or proximal jejunum. It is most prevalent at seventh decade. Jaundice, bleeding, or obstruction can be the clinical signs. At CT, the diagnosis arises from a polypoid or intramural mass site, typically in the second or third portions of duodenum (Fig. 15). MR can show a soft-tissue mass or thickening of duodenal wall too. It is usually diagnosed in the advanced stage with more than 50% of patients having nodal metastasis at the time of diagnosis, although the 5-year survival rate approaches 50%. Secondary involvement of the duodenum can occur by local involvement, as in pancreatic tumor, or metastases from distant sites as colon or ovarian carcinoma.[25,26]
– Duodenal gastrointestinal estromal tumor (GIST): GISTs are the most common mesenchymal neoplasm of the gastrointestinal tract. The best defining feature of GIST is the expression of KIT (CD117), a tyrosin kinase growth receptor. The most common clinical sign or manifestation is bleeding from ulceration mucosa or small intestine obstruction when located in gastrointestinal tract (radiographics). It represents 10–33% of overall malignant duodenal tumors, most of them located in the second or third portion of the duodenum and often with extraserosal component causing a significant mass effect over adjacent organs. On CT images, they can appear as intramural mass or endoluminal polyps (Fig. 16) or as a large well-circumscribed tumor, usually with extraluminal growing and heterogeneous enhancement with peripheral rim and low-atenuation necrotic center. Whereas lymph node enlargement is not a predominant feature, liver and peritoneum are the most common sites for distant metastasis.[27,28]
– Neuroendocrine tumor: Gastrinoma is the most common neuroendocrine tumor located in the groove and is often extrapancreatic or multiple. Most of them are located in the so-called "gastrinoma triangle", whose vertices are the

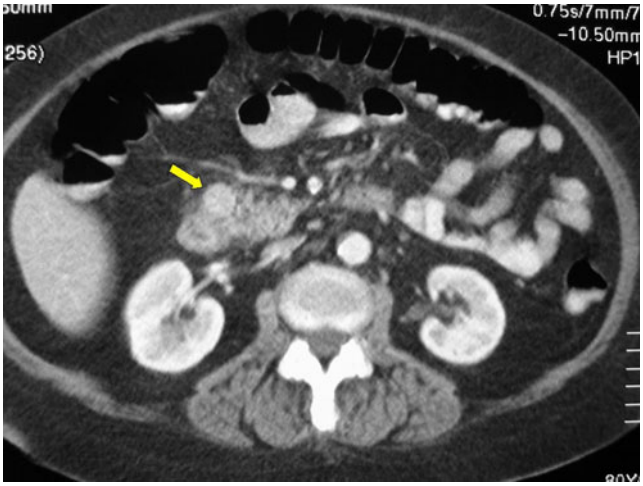

Fig. 18 Gastrinoma in pancreaticoduodenal groove. Enhanced CT scan showing small well-defined hypervascular tumor inside the gastrinoma triangle area (pancreaticoduodenal groove). The patient had Zollinger–Ellison Syndrome, and the resected tumor corresponded to a gastrinoma

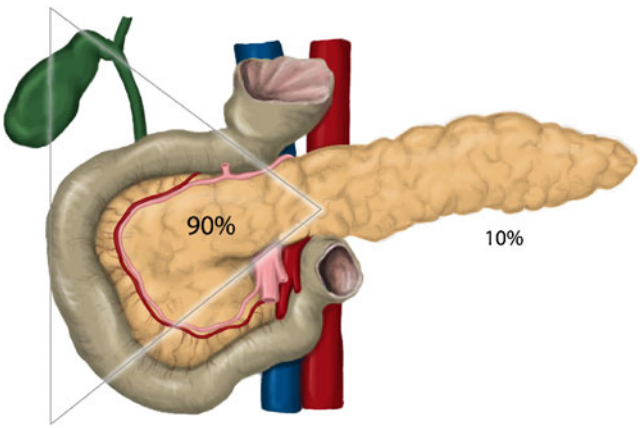

Fig. 17 Gastrinoma triangle. Schematic drawing of the gastrinoma triangle whose vertices are the cystic duct confluence, the junction of the pancreatic neck and body, and the junction of the second and third portions of the duodenum. Gastrinoma is the most common neuroendocrine tumor at the pancreatoduodenal groove

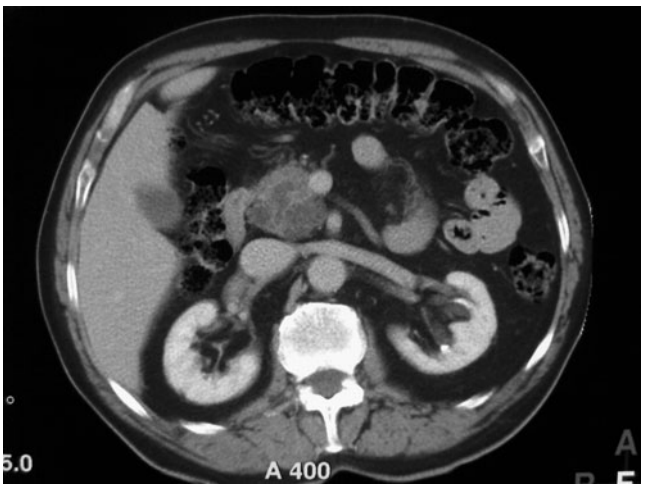

Fig. 19 Intraductal papillary mucinous tumor of the uncinate process. Enhanced CT scan shows a cystic lesion with solid component at the uncinate process

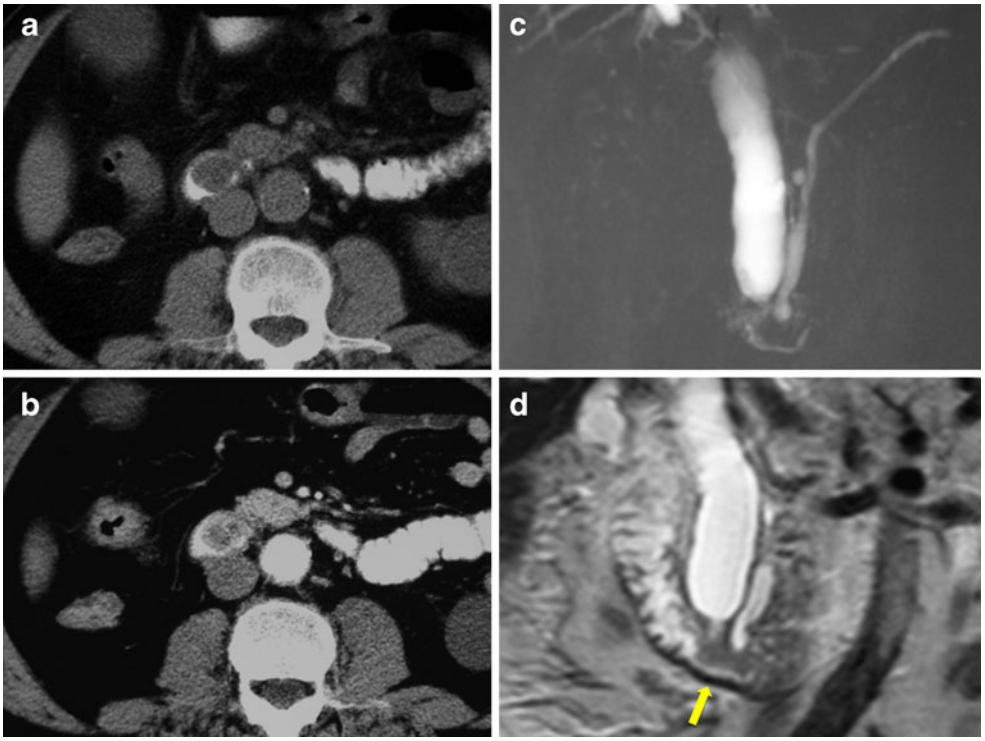

Fig. 20 Ampullary tumor. **a**–**b** Unenhanced and enhanced CT image shows an intraluminal well-defined tumor dependent from the medial duodenal wall at the level of the papilla corresponding to an ampullary tumor. **c**, **d** MR cholangiopancretography SSH SE image and coronal T2 fast SE sequence shows an important billiary tree dilatation untill the major papilla. Note the lack of dilatation of the main pancreatic duct (*yellow arrow*), the called "single duct sign" common in ampullary tumors

cystic duct confluence, the junction of the pancreatic neck and body, and the junction of the second and third portion of the duodenum[1] (Fig. 17).

Symptoms of peptic ulcer disease and diarrhea, and elevated serum levels of gastrin are present in those patients, although hypergastrinemia alone is not diagnostic.[29]

A triple-phased contrast enhancement is recommended in CT studies.[30] Its intense enhancement on CT (Fig. 18) and MR, the high signal intensity in T2-weighted sequences, and the presence of hypervascular liver metastases help to differentiate them from pancreatic adenocarcinoma.[1]

– Intraductal papillary mucinous tumor (IPMT): It refers to a spectrum of mucin-secreting proliferation of the pancreatic duct epithelium at any level of the pancreatic ductal system. IPMT has intraductal growth pattern, and the progressive duct dilatation is associated with mucin secretion.[31]

Although the tumor is usually small and flat, the entire main pancreatic duct is dilated because the mucin secretions impede the correct flow of pancreatic secretion. It is considered a low-grade

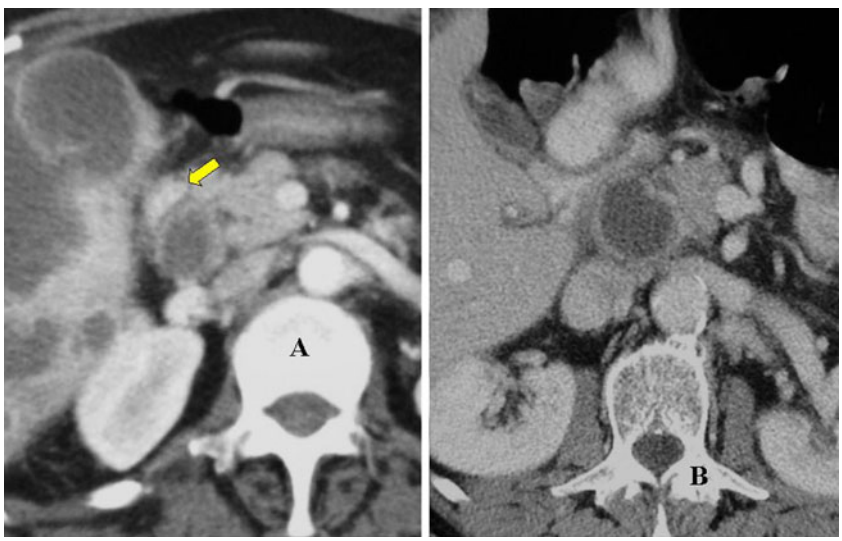

Fig. 21 Necrotic lymph nodes. **a** Shows a hypodense necrotic lymph node in the pancreaticoduodenal groove corresponding to a metastasic gallbladder squamous tumor. Note the anterior displacement of the duodenum (*arrow*). **b** Shows another necrotic hypodense lymph node corresponding to disseminated tuberculosis

malignancy, but prognosis for the different types are still not well-known. It can produce pain and laboratory abnormalities consistent with pancreatitis. It can be localized in the main pancreatic ducts or in branch ducts, the latest especially, in the branch ducts of the uncinate process, but it may be also diffuse, affecting a large number of pancreatic ducts. When it affects the uncinate process branches, it can protrude into the papilla and duodenal lumen (Fig. 19).

Total resection is the treatment of choice for the main duct type, and local resection is enough if only segmental involvement is present. Cystic lesions less than 2.5 cm and with no communication with the main duct can be followed up. Ductal nodules, intraductal mucin, and herniation of the papilla into the duodenal lumen can help to differentiate from chronic pancreatitis.[32]

– Periampullary tumors are the third most frequent gastrointestinal tumors following gastric and colorectal tumors. They arise 2 cm from the ampulla and comprise carcinoma of the ampulla, distal common bile duct, pancreas, and duodenum. They share similar clinical presentation, anatomic location, and therapeutic approaches, but the long-term outcome depends on the specific type. Presurgical staging depends on infiltration of surrounding tissue, and differentiation among them is important for treatment planning. Both CT and MR can be used to evaluate local invasion to choose the most accurate treatment.

  Ampullary carcinoma and distal bile duct carcinoma can be seen as a small mass, bulging or not, into the papilla, or periductal thickening (Fig. 20) while a pancreatic hypoattenuating mass is typical of pancreatic carcinoma. Dilatation of two proximal and two distal pancreatic or biliary ducts or the side pancreatic branches orientate to pancreas origin whereas proximal biliary duct dilatation with normal distal bile duct and no dilated pancreatic duct is seen in distal bile carcinoma. Duodenal carcinomas present only a minimum or absent bile or pancreatic duct dilatation.[25]

  The prognosis of ampullary carcinoma and duodenal periampullary carcinoma is better than bile distal ducts and pancreatic carcinoma. The small size at diagnosis and the early symptoms due to the localization and the intraluminal growth are some of the reasons of the better prognosis of ampullary carcinoma, and the rare extraluminal extension and perineural or lymphatic spread contributes too.[33,34]

– Lymph nodes: small lymph nodes in the groove is an usual finding in both hepatopancreatic CT and MR. Spread from distant malignancies to duodenopancreatic lymph nodes is common and difficult to differentiate from primary local tumors. Liver, biliary tract, pancreas, and duodenum disease may cause lymph node enlargement (Fig. 21a). Lymphoma and local inflammation can involve groove lymph nodes.[26]

  Lymphadenopathy below the level of renal veins favors the diagnosis of lymphoma in front of local neoplasm. Inflammatory diseases include rare entities as a sarcoidosis or Castleman disease. Concomitant liver or spleen lesions are seen in the first, while the second one presents with intense enhancement adenopathy.[35]

  Due to the increase prevalence both inmunocompetent and inmunocompromised patients, tuberculosis is a disease to consider. As lymphadenopathy is the most common manifestation of abdominal tuberculosis, large and multiple central low-density nodes, often accompanying large nodes in other abdominal locations, makes tuberculosis the most likely diagnosis in this case. The hypoattenuating center with hyperattenuating rim are characteristics of caseous necrosis[36] (Fig. 21b).

Conclusion

CT and MR are the most appropiate imaging modalities to evaluate pancreatoduodenal junction. The knowledge of normal anatomy, most frequent variants, and the imaging features of the different entities that involve this small anatomic area is crucial to reach the right diagnosis and treatment.

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GI IMAGE

MR Imaging of Reactive Lymphoid Hyperplasia of the Liver

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Abstract
Introduction Reactive lymphoid hyperplasia, also known as pseudolymphoma or nodular lymphoid lesion of the liver, is a rare benign lesion. It is mainly detected in the lung, stomach, small intestine, orbit, pancreas, skin, and breast. It remains difficult to distinguish reactive lymphoid hyperplasia from malignant disease clinically when it develops in the liver.
Case Report We have recently encountered a patient with liver reactive lymphoid hyperplasia who had undergone colon cancer surgery.
Conclusion Preoperative MR imaging showed some useful findings indicating reactive lymphoid hyperplasia.

Keywords Reactive lymphoid hyperplasia · Nodular lymphoid lesion · Liver · MR imaging · Diagnosis

A 68-year-old woman with a history of tuberculosis was referred to our hospital for further evaluation of a hepatic tumor detected by routine postoperative follow-up after curative resection of colon cancer (pT2 pN0) at another hospital. The patient was asymptomatic, and physical examination revealed no remarkable abnormality. Blood cell counts and serochemical findings, including liver enzymes, were within normal limits. The hepaplastin test, results for prothrombin time, and partial thromboplastin time were all normal. Hepatitis B virus surface antigen and hepatitis C virus antibody were both negative, and the levels of tumor markers, such as, α-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9, were all within the normal limits. Abdominal ultrasonography (US) showed a hypoechoic lesion in the segment 5 of the liver, 15 mm in diameter, and computed tomography (CT) showed it as a low-density lesion. It was mixed hypointense and slightly hypointense on T1-weighted images of magnetic resonance (MR) imaging and hyperintense on the T2-weighted images. On gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MR images acquired during the arterial phase, the lesion showed two components: a round portion showed minimal enhancement and the adjacent wedge-shaped area appeared isointense compared to the surrounding liver parenchyma. The former showed washout and became distinctly hypointense on portal venous phase and hepatobiliary phase, while the latter showed mild washout and became slightly hypointense. On T2-weighted images, the hyperintense areas were also seen along the portal veins, and minimal ascites was observed over the lesion. Diffusion-weighted images (DWI) showed a strongly decreased area of diffusion in the nodular portion and a decreased area of wedge shape in the adjacent parenchyma.

Given these MR findings, a benign hepatic nodule such as an inflammatory pseudotumor was highly suspected, but a metastatic tumor of colon cancer could not be ruled out. After obtaining informed consent, the hepatic lesion was surgically resected. At laparotomy, a small nodule, and depressed area could be identified on the liver surface

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resembling the MR findings (Fig. 1, 2). The patient's postoperative course was uneventful. Grossly, the resected liver segment contained a well-circumscribed, white, non-encapsulated solitary nodule measuring 1.0×0.8×0.8 cm. Microscopically, the lesion was composed of polymorphous lymphoplasmacytic infiltration with various sized and shaped lymphoid follicles, and lymphocytic infiltration was seen in the portal tracts around the nodular lesion (Fig. 2). A genetic investigation of clonality in the immunoglobulin heavy chains (IgH) using a polymerase chain reaction method with DNA from paraffin-embedded tissue revealed no clonal IgH gene rearrangement. The lesion was diagnosed as reactive lymphoid hyperplasia (RLH) of the liver.

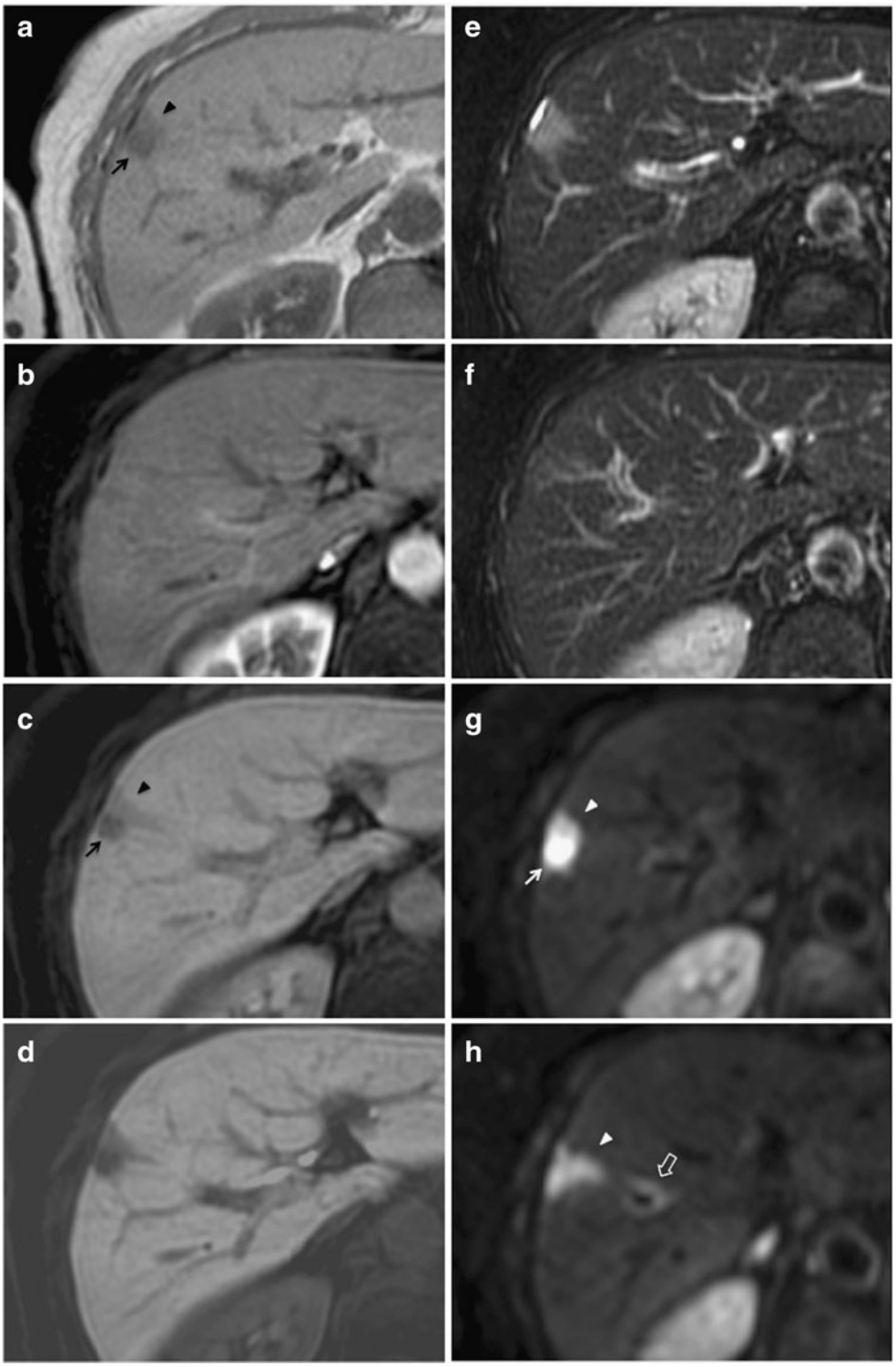

Fig. 1 MR imaging of the liver. T1-weighted image **a** shows a mixed low-intensity nodular lesion (*arrow*) and slightly low-intensity area (*arrowhead*). **b** The latter shows mild arterial enhancement on post-Gd-EOB-DTPA T1-weighted image, **c** followed by mild washout (*arrowhead*) on the portal phase image and **d** hepatobiliary phase image, while the former shows washout (*arrow*). T2-weighted images **e, f** show homogeneously high-intensity lesion with minimal ascites and edematous Glisson's capsule adjacent to the lesion. Diffusion-weighted images **g, h** show a hyperintense nodular lesion (*arrow*) and high-intensity area of wedge shape (*arrowhead*), which extends from the lesion along the vessel (*thick arrow*)

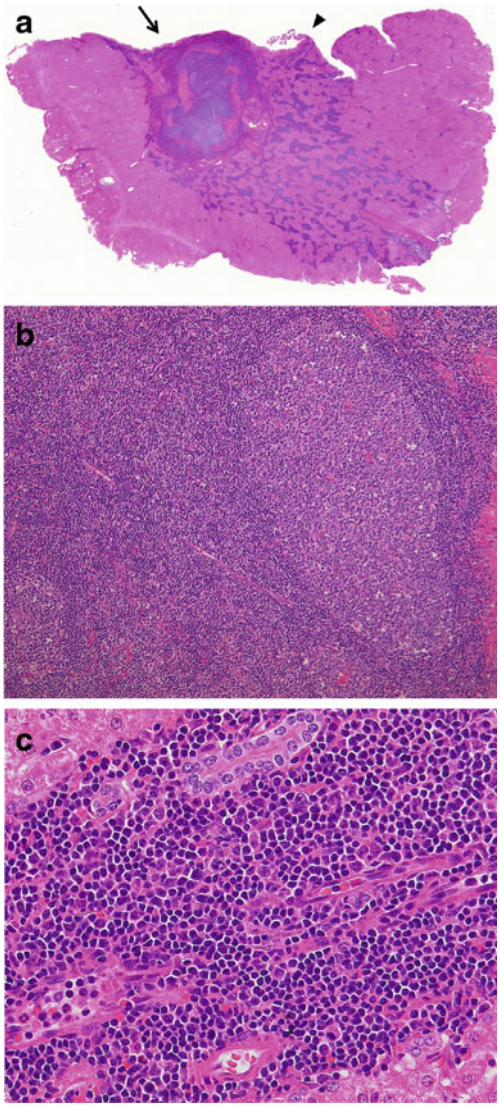

Fig. 2 Microscopically, the nodular portion is composed of polymorphous lymphoplasmacytic infiltration with various sized and shaped lymphoid follicles (*arrow* in **a**) (**a** H & E, ×2.5; **b** H & E, ×40), and the adjacent liver parenchyma shows lymphocytic infiltration in the portal tracts around the nodular lesion (*arrowhead* in **a**) (**c** H & E, ×100)

Discussion

Recent advances in imaging modalities have resulted in more frequent detection of small nodular lesions in the liver. These progresses, however, may sometimes have negative effects such as overdiagnosis. RLH, also known as pseudolymphoma or nodular lymphoid lesion of the liver, is one such lesion. Only 33 cases of hepatic RLH (including ours) have been reported in the English and Japanese literatures.[1] However, in recent years, a growing number of such reports suggests it may be more common than previously thought. It remains difficult to distinguish RLH from malignant disease clinically when it develops in the liver.

RLH is a benign nodular lesion mainly detected in the lung, stomach, small intestine, orbit, pancreas, skin, and breast. Histopathologically, it is characterized by marked proliferation of non-neoplastic, polyclonal lymphocytes forming follicles with an active germinal center.[2] Reported male–female ratio of hepatic RLH was 1:9.7, with the mean age of 55 years.[1] Although the precise etiology and pathogenesis of the disorder is still unknown, it is speculated that the etiology of the disorder is a reactive immunological response to a chronic infection or inflammation.[1, 2] Indeed, the disorder seems to develop with autoimmune diseases,[3, 4] malignancy,[2, 5] hepatitis,[6] or interferon therapy.[1, 7] Histopathologically, it is characterized by marked proliferation of non-neoplastic, polyclonal lymphocytes forming follicles with active germinal centers. When it develops in the liver, portal areas, apart from nodules, show irregular expansion with infiltration of small mature lymphocytes.[2, 5, 8, 9]

RLH has been often diagnosed as a malignant tumor preoperatively, since the imaging findings seem to be compatible with those of hepatocellular carcinoma. It is detected as a hypoechoic mass on US, a low-density lesion on CT with mild to moderate enhancement, and a non-specific lesion with MR imaging, that is, hypointense on T1-weighted images and hyperintense on T2-weighted images.[5, 8, 9] In addition to these findings, in the present case, signal changes were seen in the adjacent liver parenchyma of wedge shape extending from the lesion along the portal veins on T2-weighted images and DWI, and a different enhancement pattern of Gd-EOB-DTPA was identified (Fig. 1). These findings might represent massive lymphocyte filling within the nodular portion causing architectural distortion and focal infiltration of lymphocytes around the portal areas causing slight edematous changes and decrease of diffusion property, which is one of the characteristics of RLH.[2, 5, 8, 9]

Differentiating among various intrahepatic lesions by imaging criteria can sometimes be difficult, particularly in distinguishing between benign and malignant lesions that often have overlapping image characteristics. Arriving at a definitive or more clinically helpful diagnosis of a focal liver lesion can help reduce unnecessary invasive procedures. Therefore, understanding the underlying pathophysiology of these liver lesions may lead to better understanding of characteristic imaging manifestations, which will better direct the diagnosis. We believe that the present case might give useful information to diagnose hepatic RLH by MR imaging, including Gd-EOB-DTPA enhancement.

In conclusion, RLH of the liver appears unique in its female preponderance and associated diseases. If a liver lesion like this is found in a middle-aged woman with an inflammatory disease, the possibility of RLH should be considered.

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GI IMAGE

Primary Oesophageal Malignant Melanoma

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Abstract
Introduction Primary oesophageal malignant melanoma is an extremely rare disease. While this aggressive tumour is generally considered to have a dismal prognosis, long-term survival can be achieved by radical resection in selected cases.
Conclusions We report two cases of primary oesophageal malignant melanoma treated with Ivor–Lewis oesophagogastrectomy and review the literature.

Keywords Oesophagus · Melanoma · Surgery

Primary oesophageal malignant melanoma is extremely rare with an incidence of 0.0036 cases per million population per year, accounting for 0.1–0.2% of oesophageal cancers.[1,2] Since the identification of scattered mucosal melanocytes within 4% of normal oesophagi at post-mortem examination it has been accepted that malignant melanoma may arise as a primary tumour of the oesophagus.[3] While the underlying aetiology of the disease is uncertain the presence of melanocytosis may be a predisposing factor.[4] This aggressive tumour has a poor prognosis, but long-term survival can be achieved by radical resection in selected cases.

We describe the case of a 75-year-old man who presented with a 3-month history of progressive painless dysphagia and had a 5-cm exophytic tumour arising from the middle third of the oesophagus on endoscopic examination. Biopsies were consistent with malignant melanoma and the absence of cutaneous, ocular or mucosal melanotic lesions suggested a primary tumour rather than a secondary deposit.

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The majority of patients with primary oesophageal malignant melanoma are symptomatic at presentation, usually with dysphagia which may be accompanied by weight loss, epigastric pain and melaena. The duration of symptoms prior to diagnosis is typically around 3 months. Endoscopically, oesophageal melanomas appear as intraluminal, polypoid, irregular and (usually, although not exclusively) pigmented masses covered with intact mucosa.[2] Almost 90% of cases of oesophageal melanoma occur in the middle or distal third of the oesophagus, probably because of the greater concentration of melanocytes in this region.[5] At endoscopy amelanocytic lesions (accounting for 10–25% of cases) may be confused with epithelial carcinomas, although the latter are more likely to occur in the proximal third of the oesophagus.[6] Satellite tumour nodules have been reported in 12% of patients.[2]

The yield of whole-body CT scanning in discovering distant metastases of primary cutaneous melanoma in asymptomatic individuals is low.[7] While fluorodeoxyglucose positron emission tomography (FDG-PET) is of proven value in the detection of metastases in these patients (changing planned clinical management in up to 22% of patients) its utility in oesophageal melanoma is unclear.[8] FDG-PET imaging of our patient (Fig. 1) demonstrated no evidence of adjacent nodal disease, however it is accepted that micrometastases and lesions <10 mm may not be detected.

An Ivor–Lewis oesophagogastrectomy was performed (Fig. 2a). Histology confirmed a 7×4×3-cm malignant melanoma with adjacent melanoma in-situ and satellite lesions that are visible on gross examination of the

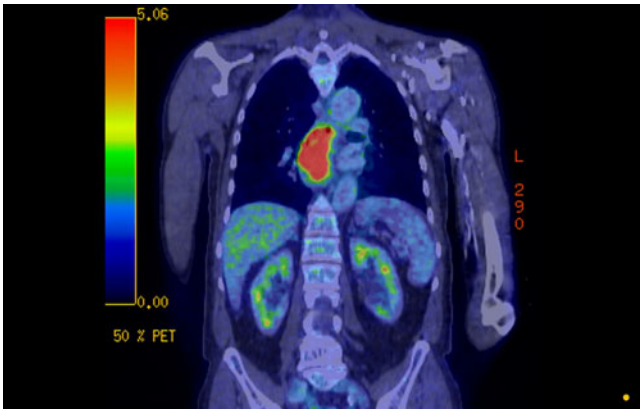

Fig. 1 FDC-PET image of a highly metabolically active malignant melanoma mass involving the oesophagus with no other sites of disease

specimen (Fig. 2b). The presence of melanin granules with junctional melanocytic activity (Fig. 3a) indicated that this was a primary tumour. There was infiltration into submucosa and focal lymphovascular invasion. Immunohistochemical positivity for S-100 protein (Fig. 3b) revealed metastatic melanoma in four of 15 lymph nodes.

Primary oesophageal malignant melanoma is an aggressive disease with almost half of patients presenting with synchronous systemic metastases secondary to haematogenous and lymphatic dissemination.[2] Positive lymph node status correlates with poor survival. Interestingly, while the incidence of perioesophageal lymph node metastasis at presentation may be as high as 66% it is unrelated to the depth of tumour invasion.[9] The prognosis is generally poor with only about one third of patients surviving beyond 12 months and a 5-year survival rate of less than 5%.[2] Total or near-total oesophagectomy is the preferred treatment for operable patients, raising the 5-year survival to 37%.[5] The mean survival after local resection of only 9 months is a reflection of the longitudinal spread of tumour along the submucosa necessitating a wider margin of resection.[2] The role of chemotherapy in the adjuvant and neoadjuvant setting is not well defined with only sporadic reports of response and the value of newer treatment modalities such as intraluminal brachytherapy and laser photoablation remains to be established. When surgical resection of the tumour is not feasible external beam radiotherapy may provide good palliation of symptoms.[10]

Our patient remains well 2 months following surgery. Remarkably, considering the rarity of this disease, we had earlier experience of treating primary oesophageal malignant melanoma in a 77-year-old man. This patient had an 11×3-cm tumour treated with Ivor–Lewis oesophagogastrectomy. Despite tumour infiltration through

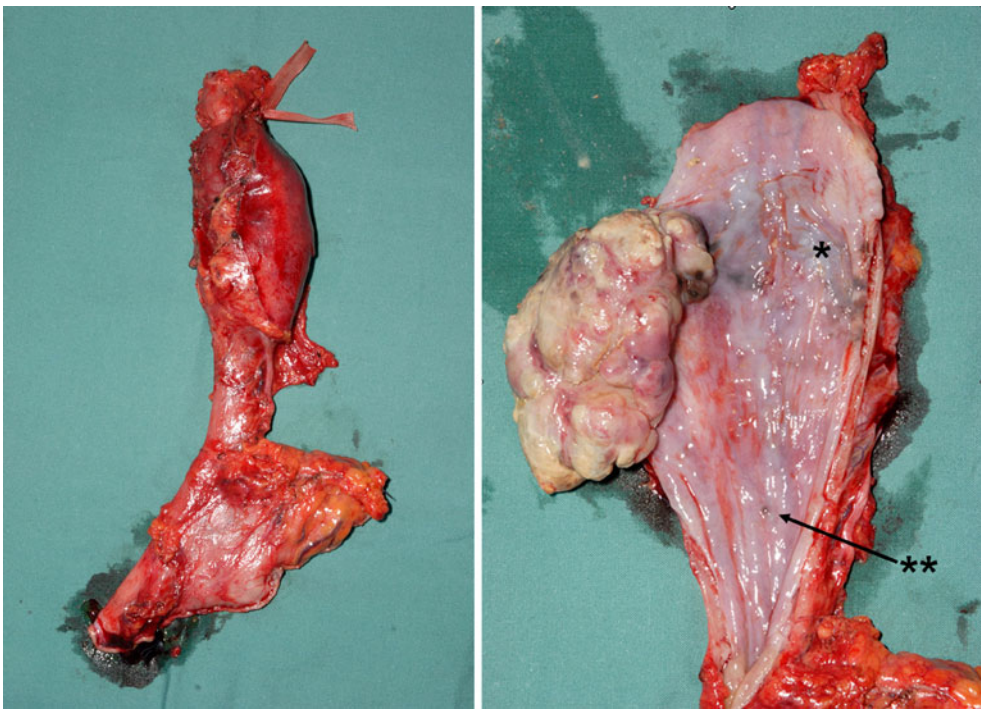

Fig. 2 Surgical specimen showing **a** extent of resection and **b** opened demonstrating melanoma in situ (*asterisk*) and satellite lesion (*double asterisks*)

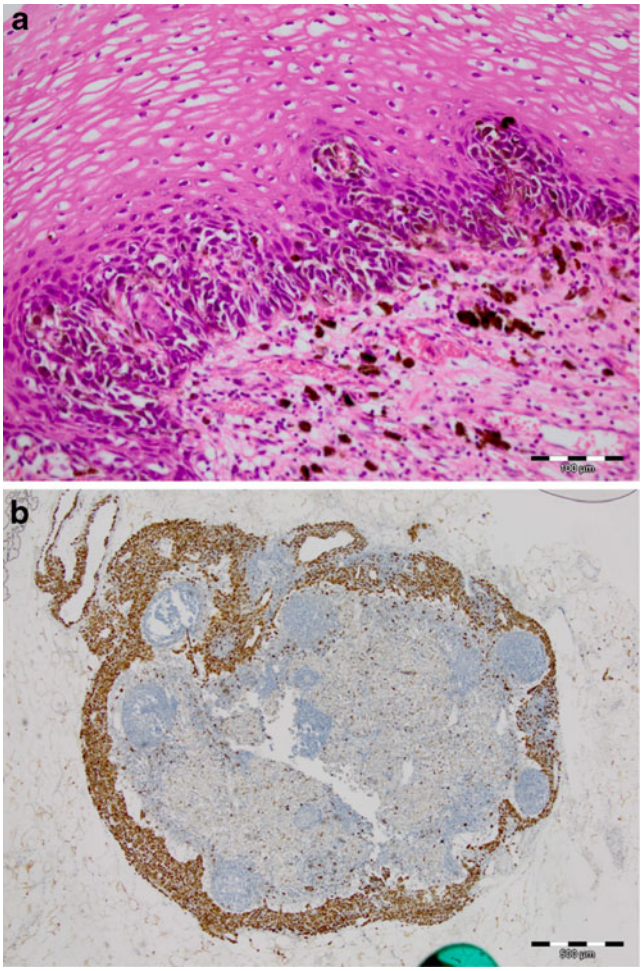

Fig. 3 **a** Junctional melanocytic activity; **b** lymph node positive for S-100 protein immunohistochemical staining

the full thickness of the oesophageal wall he had node-negative disease and remains well 22 months following surgery.

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GI IMAGE

Gastrointestinal Image: A True Giant Transverse Colon Diverticulum

Marek Olakowski · Beata Jabłońska · Andrzej Lekstan · Weronika Szczęsny-Karczewska · Joanna Pilch-Kowalczyk · Maciej Kohut

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Abstract Giant colonic diverticulum is an extremely rare condition in colonic diverticular disease. More than 90% of giant colonic diverticula are found in the sigmoid colon. Inflammatory and pseudodiverticula are the most frequent. Only one case of a true diverticulum of the transverse colon has been reported in the literature.
Case Report We report a case of a 22-year-old woman presenting with constipation and meteorism from childhood. A plain abdominal X-ray showed a round radiolucent air-filled cyst. Barium enema revealed a single, large diverticulum of the transverse colon. An extended right hemicolectomy with primary end-to-end anastomosis was performed. The postoperative course was uneventful, and she was discharged in 1 week without any complications. Histopathology showed a true diverticulum containing all layers of the colon.

Keywords Giant colonic diverticulum · Transverse colon · Congenital duplication

Case History

In July 2010, a 22-year-old woman was admitted with a history of constipation and meterorism that were long-standing from childhood. The loss of weight and anorexia secondary to restricted diet appeared several years ago. She underwent appendectomy at the age of 1 year. She had been previously diagnosed in other departments, and based on colonoscopy, dolichocolon had been suggested. Physical examination revealed a large abdominal mass and cachexia (BMI=15.5 kg/m^2). A plain abdominal X-ray showed a round radiolucent air-filled cyst. Barium enema revealed a single, large diverticulum of the transverse colon (Fig. 1). Laparotomy showed a giant diverticulum originating from the proximal part of the transverse colon that was 40 cm long, 10–15 cm wide at the bottom and 4–5 cm wide at the gate (Fig. 2). The right half of the colon was dilated and had flabby walls. An extended right hemicolectomy with primary end-to-end anastomosis was performed. Histopathology revealed that the giant diverticulum contained all four layers of the normal bowel wall (Fig. 3). The postoperative course was uneventful, and she was discharged in 1 week without any complications.

Discussion

A giant colonic diverticulum (GCD) is defined as a colonic diverticulum measuring 4 cm or larger.[1,2] It is a very rare condition, and most frequently, it is associated with colonic diverticular disease. More than 90% of giant colonic

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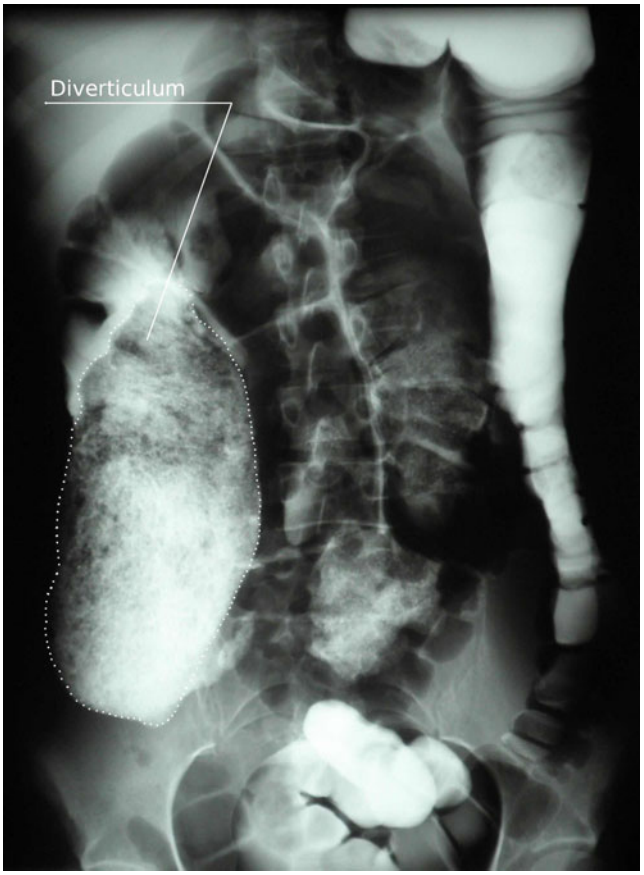

Fig. 1 Barium enema showing a giant diverticulum of the transverse colon

diverticula are found in the sigmoid colon. GCD was described first in 1953 by Hughes and Greene,[3] primarily as a "solitary air cyst". Different names ("giant air cyst" or "giant cyst") have been used to describe this condition. According to Steenvoorde et al.,[2] the term "giant colonic diverticulum" is preferred. Pathologically, GCD is divided into three types: type I (22%), pseudodiverticulum composed of granulation and fibrous tissue, with chronic inflammatory cells and remnants of muscularis mucosa; type II (66%), inflammatory diverticulum arising from local perforation and communicating with an abscess cavity and type III (12%), true diverticulum that contains all the layers of normal bowel wall and being in continuity with the gut lumen.[2,4] Giant diverticulum located in the transverse colon is extremely rare.[5–7] Only one case of a true giant diverticulum of the transverse colon that was accompanied by a right inguinal hernia of the greater omentum has been reported in the literature.[5]

We present the unique case of an uncomplicated true giant diverticulum of the transverse colon. Because symptoms have been remaining from patient's childhood, we believe that this pathology can be congenital due to an intestinal duplication.

GCD may be asymptomatic or presents with nonspecific symptoms, such as vague abdominal pain, constipation, rectal bleeding, nausea and vomiting, abdominal distension, diarrhoea and abdominal mass.[2] In 28% of patients, complications such as inflammation, perforation, intra-abdominal abscess formation and wall infarction occur. A 2% risk of carcinoma developing inside diverticulum has been reported in the literature. [4] A plain supine abdominal X-ray is the radiological investigation of choice for GCD diagnosis.[2] Preoperative diagnosis may also include barium enema, CT scan or MRI.[5,8]

Diverticulectomy in selected cases or partial colectomy with the diverticulum is the preferred method of treatment in uncomplicated GCD. In complicated cases, a two-stage resection with Hartmann procedure is necessary.[8]

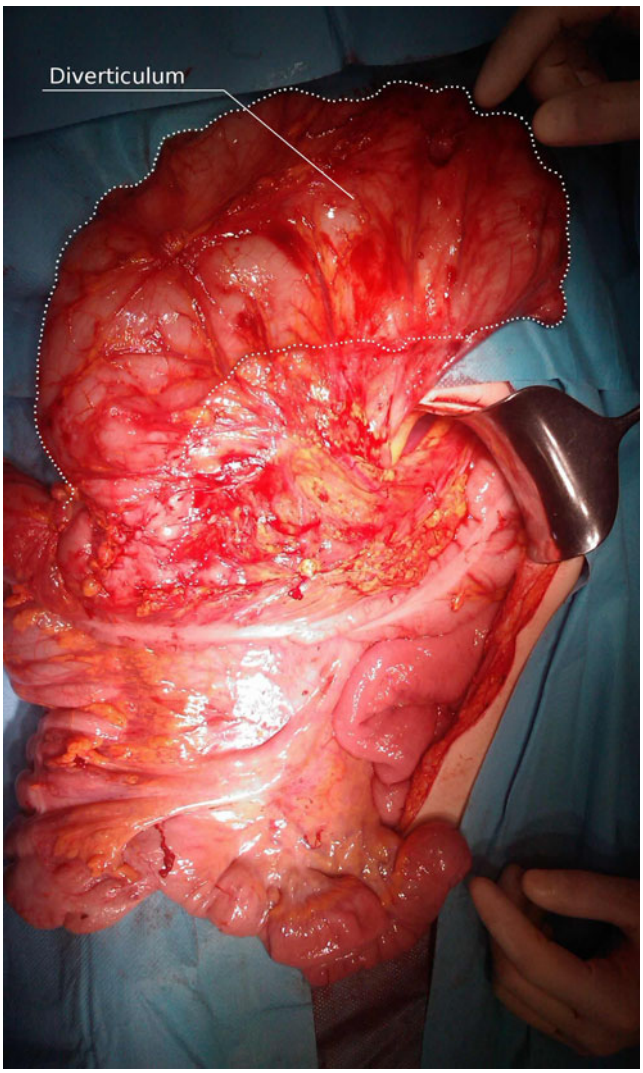

Fig. 2 Intraoperative image demonstrating a giant diverticulum of the transverse colon

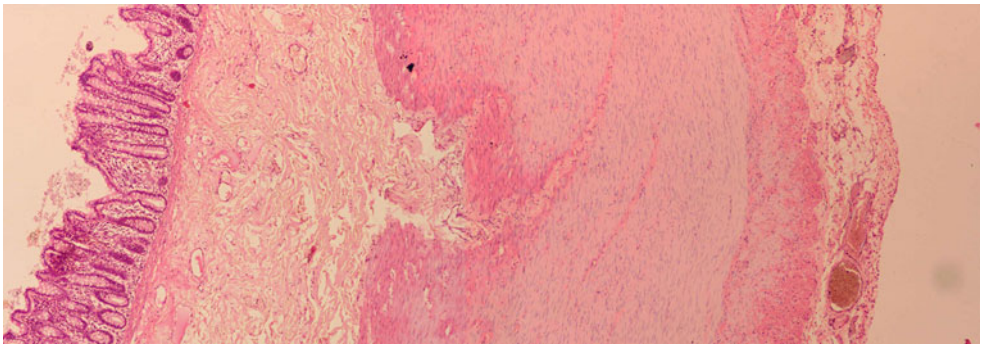

Fig. 3 Histopatological examination—a giant diverticulum contains all four layers of the normal bowel wall

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LETTER TO THE EDITOR

Interval Between Neoadjuvant Chemoradiation and Surgery for the Management of Rectal Cancer

Sergio Huerta

Received: 1 January 2011 / Accepted: 26 March 2011 / Published online: 12 April 2011

Dear Editor:

In the manuscript "Neoadjuvant Therapy for Rectal Cancer: The Impact of Longer Interval Between Chemoradiation and Surgery", Dr. de Campos-Lobato [1] continues to add evidence to the positive oncological effects of achieving a pathological complete response (pCR). [2] Additionally, their manuscript provides alternative treatment strategies in terms of timing in the trimodality (surgery, chemotherapy, and radiotherapy) approach for the management of rectal cancer. While the rate of complications was similar in both of the groups analyzed, the cohort that had a waiting interval of ≥8 weeks demonstrated a higher rate of pCR. This approach is novel and continues to add tools in the armamentarium in the management of patients affected with rectal cancer.

There are, however, a few issues that remain at large: (1) how can we identify the patients likely to response to neoadjuvant modalities? Our experience shows that up to 50% of patients show a partial response; while, over 20% do not respond to this strategy and, in fact, the tumor continues to grow. [3] Thus, waiting longer clearly benefits the segment of the patients that achieve a pCR, but how can we identify this cohort patients preoperatively? (2) The 8-week period mark stems from the group's previous work, [4] in which a longer interval was an independent predictor for pCR. However, can we wait even longer (10 to 12 weeks)? Will a longer interval even result in a superior rate of pCR? What should the limit be? Thus, we need randomized trials to assess the best interval for surgical intervention following neoadjuvant chemoradiation. Preclinical studies might also suggest a time interval for the best tumor response. (3) Should chemotherapy be continued during the interval period? We should exercise caution in widening the interval prior to surgical intervention as some patients might experience tumor growth during treatment. These patients should at least undergo restaging strategies at a given interval between the waiting period of neoadjuvant chemoradiation and surgical intervention. This interval is also best addressed in the context of a randomized control trial.

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LETTER TO THE EDITOR

Response to Letter to the Editor: Neoadjuvant Therapy for Rectal Cancer: The Impact of Longer Interval Between Chemoradiation and Surgery

Luiz Felipe de Campos-Lobato · Daniel P. Geisler · André da Luz Moreira · Luca Stocchi · David W. Dietz · Matthew F. Kalady

Received: 23 February 2011 / Accepted: 26 March 2011 / Published online: 15 April 2011

To the Editors:

We thank Dr. Huerta for his kind words and thoughtful comments on our recent article.[1] He brings forth several key issues that remain among the top challenges in treating rectal cancer. We agree that it would obviously be paramount to identify which patients would achieve a pathologic complete response (pCR), but unfortunately this is not currently possible. Indeed, our group and others are currently investigating possible genetic markers to potentially identify which patients are most likely to achieve pCR, but only the future will tell. As Dr. Huerta states, the interval of 8 weeks for analysis in this study was chosen from our previous work which identified that waiting at least 8 weeks was independently associated with a higher percentage of patients achieving pCR.[2] This was a non-randomized, retrospective study and the exact interval that would be most effective remains undefined. A well-designed trial is necessary to accurately address this matter and an ongoing NIH-sponsored multicenter prospective trial[3] is enrolling approximately 250 rectal cancer patients into one of five different treatment groups based on an increasing interval between completion of neoadjuvant therapy and surgery. The intervals being examined are 6, 12, 16, 20, and 24 weeks and the study is expected to complete enrollment within this year. Patients in the longer interval treatment arms will receive chemotherapy during the waiting period. Results of this trial will answer some of the critical issues regarding intervals between neoadjuvant chemoradiation and surgery.

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LETTER TO THE EDITOR

Letter

Published online: 11 May 2011

To the Editor,

I read the May 2010 GI Image by Harb with interest in light of our recent publication on a similar topic.[1] In this case report, they described a patient in multi-organ failure with small bowel pneumatosis and superior mesenteric and portal venous gas. The authors clearly demonstrated dramatic images of gas within the bowel wall and liver, which have often led clinicians to suspect an abdominal catastrophe.

The authors define *portal pyemia* as a combination of infection and thrombosis of the portal vein. Unfortunately, the selected images failed to demonstrate thrombosis of the portal vein, and the laparotomy failed to identify clot in the superior mesenteric or portal vein. The subsequent autopsy also failed to document thrombosis of the mesenteric or hepatic veins. Why did the authors maintain a thrombosis theory when all proof was to the contrary? No positive cultures were found in perioperative period, at surgery, and at autopsy. They attribute the failure to obtain positive cultures to bacterial clearance within the liver and potent antibiotics. Why did the authors not acknowledge that they may have been dealing with a nonbacterial phenomenon?

In March 2010 journal, we describe our experience with pneumatosis and portal vein gas in over 88 patients treated at the University of Iowa. We found that in a large percentage of patients (30%), there exists NO intra-abdominal pathology. In many cases, a laparotomy may be necessary to "rule out" common intra-abdominal catastrophes. But when a laparotomy is non-revealing and therefore nontherapeutic, the clinicians must be capable of looking beyond the "gas" and vigorously explore and treat alternative diagnosis.

Sincerely,

Neal Wilkinson

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