

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2016 September 27; 8(9): 598-659





Editorial Board

2016-2019

The *World Journal of Gastrointestinal Surgery* Editorial Board consists of 332 members, representing a team of worldwide experts in pediatrics. They are from 37 countries, including Argentina (1), Australia (6), Austria (2), Belgium (6), Brazil (9), Bulgaria (2), Canada (7), China (30), Finland (2), France (9), Germany (22), Greece (7), India (11), Ireland (3), Israel (3), Italy (46), Jamaica (1), Japan (46), Lithuania (1), Malaysia (1), Netherlands (11), Pakistan (1), Poland (1), Portugal (1), Russia (1), Saudi Arabia (1), Serbia (2), Singapore (3), South Korea (8), Spain (5), Sweden (1), Switzerland (3), Thailand (2), Tunisia (1), Turkey (9), United Kingdom (11) and United States (56).

EDITOR-IN-CHIEF

Timothy M Pawlik, *Baltimore*

ASSOCIATE EDITORS

Giovanni Dapri, *Brussels*
Dietrich Doll, *Vechta*
Antonello Forgione, *Milan*
Urs Florian Giger, *Herne*
Dogan Gonullu, *Istanbul*
Wai-Lun Law, *Hong Kong*
Amjad Parvaiz, *Portsmouth*
Mariano Palermo, *Buenos Aires*

GUEST EDITORIAL BOARD MEMBERS

Chien-Hung Chen, *Taipei*
Hsin-Yuan Fang, *Changhua*
Jong-Shiaw Jin, *Taipei*
Chen-Guo Ker, *Kaohsiung*
King-Teh Lee, *Kaohsiung*
Wei-Jei Lee, *Taoyuan*
Wan-Yu Lin, *Taichung*
Yan-Sheng Shan, *Tainan*
Yau-Lin Tseng, *Tainan*
Jaw-Yuan Wang, *Kaohsiung*
Jaw-Yuan Wang, *Kaohsiung*
Li-Wha Wu, *Tainan*

MEMBERS OF THE EDITORIAL BOARD



Australia

Ned Abraham, *Coffs Harbour*
Robert Gibson, *Victoria*
Michael Michael, *Victoria*
DL L Morris, *Sydney*
Jaswinder Singh Samra, *Leonards*

Matthias Wilhelm Wichmann, *Mount Gambier*



Austria

Harald R Rosen, *Vienna*
Franz Sellner, *Vienna*



Belgium

Jean-Francois Gigot, *Brussels*
Lerut Jan Paul Lerut, *Brussels*
Gregory Peter Sergeant, *Leuven*
Hans Van Vlierberghe, *Gent*
Jean-Louis Vincent, *Brussels*



Brazil

Jose Eduardo Aguilar-Nascimento, *Cuiaba*
Mario Reis Alvares-da-Silva, *Porto Alegre*
Fernando Mart n Biscione, *Minas Gerais*
Julio CU Coelho, *Curitiba*
Jos  Sebastiao dos Santos, *Ribeirao Preto*
Marcel Autran C Machado, *Sao Paulo*
Marcelo AF Ribeiro, *Sao Paulo*
Marcos Vinicius Motta Valadao, *Rio de Janeiro*
Ricardo Zorron, *Rio De Janeiro*



Bulgaria

Nikolai Vasilev Belev, *Plovdiv*
Krasimir Dimitrov Ivanov, *Varna*



Canada

Runjan Chetty, *Toronto*

Laura Ann Dawson, *Toronto*
Mahmoud A Khalifa, *Toronto*
Peter CW Kim, *Ontario*
Peter Metrakos, *Montreal*
Reda S Saad, *Toronto*
Manuela M Santos, *Montreal*



China

Yue-Zu Fan, *Shanghai*
Wen-Tao Fang, *Shanghai*
Yong-Song Guan, *Chengdu*
Shao-Liang Han, *Wenzhou*
Michael G Irwin, *Hong Kong*
Long Jiang, *Shanghai*
Wei Li, *Changchun*
Ting-Bo Liang, *Hangzhou*
Quan-Da Liu, *Beijing*
Yu-Bin Liu, *Guangdong*
John M Luk, *Hong Kong*
Jian-Yang Ma, *Chengdu*
Kwan Man, *Hong Kong*
Tang Chung Ngai, *Hong Kong*
Yan-Ning Qian, *Nanjing*
Ai-Wen Wu, *Beijing*
Yun-Fei Yuan, *Guangzhou*



Finland

Helena Mariitta Isoniemi, *Helsinki*
Isto Henrik Nordback, *Tampere*



France

Mustapha Adham, *Lyon 03*
Nicolas Jarufe Cassis, *Paris*
Alain Chapel, *Fontenay-Aux-Roses*

Jean-Francois Gillion, *Antony*
 Guilhem Godlewski, *Saint Chaptes*
 Denis Heresbach, *Rennes*
 Romaric Loffroy, *Dijon*
 Jacques Marescaux, *Strasbourg Cedex*
 Aurelie Plessier, *Clichy*



Germany

Hans G Beger, *Ulm*
 Dieter C Broering, *Kiel*
 Ansgar Michael Chromik, *Bochum*
 Irene Esposito, *Neuherberg*
 Stefan Fichtner-Feigl, *Regensburg*
 Benedikt Josef Folz, *Lippspringe*
 Helmut Friess, *Munich*
 Reinhart T Grundmann, *Burghausen*
 Bertram Illert, *Würzburg*
 Jakob R Izbicki, *Hamburg*
 Tobias Keck, *Freiburg*
 Jorg Kleeff, *Munich*
 Axel Kleespies, *Munich*
 Andrew S Klein, *Hamburg*
 Uwe Klinge, *Aachen*
 Martin G Mack, *Frankfurt/Main*
 Matthias Peiper, *Düsseldorf*
 Hubert J Scheidbach, *Magdeburg*
 Joerg Theisen, *Munich*
 Brigitte Vollmar, *Rostock*



Greece

Teni Bouliskas, *Athens*
 Elco de Bree, *Heraklion*
 Stavros Gourgiotis, *Athens*
 Andreas Manouras, *Athens*
 Theodoros E Pavlidis, *Thessaloniki*
 George H Sakorafas, *Athens*
 Vassilios Smyrniotis, *Athens*



India

Anil Kumar Agarwal, *New Delhi*
 Samik Kumar Bandyopadhyay, *Kolkata*
 Somprakas Basu, *Varanasi*
 Pravin Jaiprakash Gupta, *Nagpur*
 Vinay Kumar Kapoor, *Lucknow*
 Chandra K Pandey, *Lucknow*
 Shailesh V Shrikhande, *Mumbai*
 Sadiq Saleem Sikora, *Bangalore*
 Rakesh Kumar Tandon, *New Delhi*
 Shams ul Bari, *Kashmir*
 Imtiaz Ahmed Wani, *Kashmir*



Ireland

Kevin CP Conlon, *Dublin*
 Prem Puri, *Dublin*
 Eamonn MM Quigley, *Cork*



Israel

Ariel Halevy, *Zerifin*
 Jesse Lachter, *Haifa*
 Hagit Tulchinsky, *Tel Aviv*



Italy

Angelo Andriulli, *San Giovanni Rotondo*
 Giuseppe Aprile, *Udine*
 Gianni Biancofiore, *Pisa*
 Stefania Boccia, *Rome*
 Luigi Bonavina, *Milano*
 Pier Andrea Borea, *Ferrara*
 Giovanni Cesana, *Milano*
 Stefano Crippa, *Vimercate*
 Giovanni D De Palma, *Naples*
 Natale Di Martino, *Naples*
 Giorgio Di Matteo, *Roma*
 Giorgio Ercolani, *Bologna*
 Carlo V Feo, *Ferrara (Cona)*
 Simone Ferrero, *Genoa*
 Leandro Gennari, *Rozzano*
 Felice Giuliani, *Roma*
 Calogero Iacono, *Verona*
 Riccardo Lencioni, *Pisa*
 Fabrizio Luca, *Milano*
 Giuseppe Malleo, *Verona*
 Paolo Massucco, *Candiolo*
 Giulio Melloni, *Milan*
 Paolo Morgagni, *Forli*
 Chiara Mussi, *Rozzano*
 Gabriella Nesi, *Florence*
 Angelo Nespoli, *Monza*
 Giuseppe Nigri, *Rome*
 Fabio Pacelli, *Rome*
 Corrado Pedrazzani, *Siena*
 Roberto Persiani, *Rome*
 Pasquale Petronella, *Napoli*
 Piero Portincasa, *Bari*
 Stefano Rausei, *Rome*
 Carla Ida Ripamonti, *Milan*
 Antonio Russo, *Palermo*
 Giulio A Santoro, *Treviso*
 Giuseppe S Sica, *Rome*
 Gianfranco Silecchia, *Faggiana*
 Mario Testini, *Bari*
 Guido Alberto Massimo Tiberio, *Brescia*
 Franco Valenza, *Milan*
 Umberto Veronesi, *Milan*
 Bruno Vincenzi, *Rome*
 Marco Vivarelli, *Ancona*
 Alessandro Zerbi, *Milan*



Jamaica

Joseph Martin Plummer, *Kingston*



Japan

Yasunori Akutsu, *Chiba*
 Ryuichiro Doi, *Kyoto*
 Yosuke Fukunaga, *Sakai*
 Akira Furukawa, *Shiga*
 Shigeru Goto, *Oita*
 Kazuhiko Hayashi, *Tokyo*
 Naoki Hiki, *Tokyo*
 Takeyama Hiromitsu, *Nagoya*
 Tsukasa Hotta, *Wakayama*
 Yutaka Iida, *Gifu City*
 Kazuaki Inoue, *Aoba-ku Yokohama*
 Masashi Ishikawa, *Tokushima*

Tatsuo Kanda, *Niigata*
 Tatsuyuki Kawano, *Tokyo*
 Keiji Koda, *Chiba*
 Tsuyoshi Konishi, *Tokyo*
 Iruru Maetani, *Tokyo*
 Yoshimasa Maniwa, *Kobe*
 Toru Mizuguchi, *Sapporo*
 Zenichi Morise, *Nagoya*
 Yoshihiro Moriwaki, *Yokohama*
 Yoshihiro Moriya, *Tokyo*
 Satoru Motoyama, *Akita*
 Hiroaki Nagano, *Osaka*
 Masato Nagino, *Aichi*
 Kazuyuki Nakamura, *Yamaguchi*
 Shingo Noura, *Osaka*
 Kazuo Ohashi, *Tokyo*
 Hirozumi Sawai, *Nagoya*
 Shouji Shimoyama, *Tokyo*
 Masayuki Sho, *Nara*
 Yasuhiko Sugawara, *Tokyo*
 Hiroshi Takamori, *Kumamoto*
 Sonshin Takao, *Kagoshima*
 Kuniya Tanaka, *Yokohama*
 Masanori Tokunaga, *Shizuoka*
 Hironori Tsujimoto, *Saitama*
 Yasunobu Tsujinaka, *Chiba*
 Akira Tsunoda, *Chiba*
 Toshifumi Wakai, *Niigata*
 Jiro Watari, *Hyogo*
 Shinichi Yachida, *Kagawa*
 Yasushi Yamauchi, *Fukuoka*
 Hiroki Yamaue, *Wakayama*
 Yutaka Yonemura, *Oosaka*
 I Yoshida, *Ishikawa*



Lithuania

Donatas Venskutonis, *Kaunas*



Malaysia

Way Seah Lee, *Kuala Lumpur*



Netherlands

Lee H Bouwman, *Leiden*
 Wim A Buurman, *Maastricht*
 Robert AFM Chamuleau, *Amsterdam*
 Miguel A Cuesta, *Amsterdam*
 Jeroen Heemskerk, *Eindhoven*
 Buis Carlijn Ineke, *Deventer*
 Wjhj Meijerink, *Amsterdam*
 Pieter Poortman, *Purmerend*
 Jan H Stoot, *Maastricht*
 Alexander Lucas Vahrmeijer, *Leiden*
 Chj van Eijck, *Rotterdam*



Pakistan

Kamran Khalid, *Lahore*



Poland

Boguslaw B Machalinski, *Szczecin*

**Portugal**

Jorge Correia-Pinto, *Braga*

**Russia**

Grigory G Karmazanovsky, *Moscow*

**Saudi Arabia**

Salman Y Guraya, *Madina Al Munawara*

**Serbia**

Ivan Jovanovic, *Belgrade*
Miroslav Nikola Milicevic, *Beograd*

**Singapore**

Francis Seow-Choen, *Singapore*
Vishalkumar G Shelat, *Jalan Tan Tock Seng*
Melissa Teo, *Singapore*

**South Korea**

Joon Koo Han, *Seoul*
Hyung-Ho Kim, *Seongnam*
Woo Ho Kim, *Seoul*
Sangyeoup Lee, *Yangsan*
Woo Yong Lee, *Seoul*
Hyo K Lim, *Seoul*
Jae Hyung Noh, *Seoul*
Sung Hoon Noh, *Seoul*

**Spain**

Antonio M Lacy, *Barcelona*
L Llado, *Barcelona*
David Parés, *Barcelona*
Jesus Prieto, *Pamplona*
Francisco Jose Vizoso, *Gijón*

**Sweden**

Helgi Birgisson, *Uppsala*

**Switzerland**

Pascal Bucher, *Geneva*
Pascal Gervaz, *Geneva*
Marc Pusztaszeri, *Carouge*

**Thailand**

Varut Lohsiriwat, *Bangkok*
Rungsun Rerknimitr, *Bangkok*

**Tunisia**

Nafaa Arfa, *Tunis*

**Turkey**

A Ziya Anadol, *Besevler*
Unal Aydin, *Izmir*
Mehmet Fatih Can, *Ankara*
Gozde Kir, *Istanbul*
Adnan Narcı, *Afyon*
Ilgin Ozden, *Istanbul*
Mesut Abdulkerim Unsal, *Canakkale*
Omer Yoldas, *Ankara*

**United Kingdom**

Simon Bramhall, *Hereford*
Brian Ritchie Davidson, *London*
Andrea Frilling, *London*
Giuseppe Fusai, *London*
Gianpiero Gravante, *Leicester*
Najib Haboubi, *Manchester*
Mohammad Abu Hilal, *Southampton*
Aftab Alam Khan, *Kent*
Federico Messina, *London*
Aravind Suppiah, *Beverleu*

**United States**

Eddie K Abdalla, *Houston*
Marc D Basson, *Grand Forks*
James M Becker, *Boston*
Thomas David Boyer, *Tucson*

Michael E de Vera, *Pittsburgh*
Elijah Dixon, *Houston*
Andrew J Duffy, *New Haven*
Kelli MB Dunn, *Buffalo*
Thomas Fabian, *New Haven*
Piero Marco Fisichella, *Maywood*
Raja M Flores, *New York*
Robert A Forse, *Omaha*
Markus Frank, *Boston*
Niraj J Gusani, *Hershey*
Douglas W Hanto, *Boston*
Scott A Hundahl, *Sacramento*
Michel Kahaleh, *Charlottesville*
David S Kauvar, *San Antonio*
Mary Margaret Kemeny, *Queens*
Vijay P Khatri, *Sacramento*
Joseph Kim, *Duarte*
Richard A Kozarek, *Seattle*
Robert A Kozol, *Farmington*
Sunil Krishnan, *Houston*
Atul Kumar, *Northport*
Keith Douglas Lillemoe, *Baltimore*
Henry Thomson Lynch, *Omaha*
Paul Ellis Marik, *Philadelphia*
Robert C Miller, *Rochester*
Thomas J Miner, *Providence*
Klaus Monkemuller, *Birmingham*
Ravi Murthy, *Houston*
Atsunori Nakao, *Pittsburgh*
Hirofumi Noguchi, *Dallas*
Jeffrey A Norton, *Stanford*
Alessio Pigazzi, *Duarte*
Mitchell C Posner, *Chicago*
KR Reddy, *Philadelphia*
Alexander Rosemurgy, *Tampa*
Alexander S Rosemurgy, *Tampa*
Sukamal Saha, *Flint*
Reza F Saidi, *Boston*
Aaron R Sasson, *Omaha*
Christian Max Schmidt, *Indianapolis*
LD Selemón, *New Haven*
Perry Shen, *Winston-Salem*
Ali Ahmed Siddiqui, *Texas*
Frank A Sinicrope, *Rochester*
John H Stewart, *Winston-Salem*
Paul H Sugarbaker, *Washington*
Douglas S Tyler, *Durham*
Vic Velanovich, *Detroit*
Michael M Wolfe, *Boston*
You-Min Wu, *Little Rock*
Zhi Zhong, *Charleston*

MINIREVIEWS

- 598** Update on medical and surgical options for patients with acute severe ulcerative colitis: What is new?
Andrew RE, Messaris E
- 606** Role of surgery for colorectal cancer in the elderly
Biondi A, Vacante M, Ambrosino I, Cristaldi E, Pietrapertosa G, Basile F
- 614** Rubber band ligation of hemorrhoids: A guide for complications
Albuquerque A
- 621** Minimally invasive management of anastomotic leaks in colorectal surgery
Sevim Y, Celik SU, Yavarifar H, Akyol C

ORIGINAL ARTICLE

Basic Study

- 627** Fibrinogen-thrombin collagen patch reinforcement of high-risk colonic anastomoses in rats
Suárez-Grau JM, Bernardos García C, Cepeda Franco C, Mendez García C, García Ruiz S, Docobo Durantez F, Morales-Conde S, Padillo Ruiz J

Retrospective Study

- 634** Total pancreatectomy: Short- and long-term outcomes at a high-volume pancreas center
Zakaria HM, Stauffer JA, Raimondo M, Woodward TA, Wallace MB, Asbun HJ
- 643** Short-term and middle-term evaluation of laparoscopic hepatectomies compared with open hepatectomies: A propensity score matching analysis
Untereiner X, Cagnet A, Memeo R, De Blasi V, Tzedakis S, Piardi T, Severac F, Mutter D, Kianmanesh R, Marescaux J, Sommacale D, Pessaix P
- 651** Barium appendicitis: A single institution review in Japan
Katagiri H, Lefor AK, Kubota T, Mizokami K

CASE REPORT

- 656** Eosinophilic ascites: A diagnostic and therapeutic challenge
Agrawal S, Vohra S, Rawat S, Kashyap V

Contents

World Journal of Gastrointestinal Surgery
Volume 8 Number 9 September 27, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Dr. Ansgar Michael Chromik, MD, Department of General and Visceral Surgery, St Josef-Hospital, University of Bochum, 44791 Bochum, Germany

AIM AND SCOPE

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJGS*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Gastrointestinal Surgery is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF

I-III Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Dan Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Shui Qiu*
Proofing Editorial Office Director: *Xin-Xia Song*

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITOR-IN-CHIEF

Timothy M Pawlik, MD, Director, Professor, Department of Surgery, Johns Hopkins University, School of Medical, Baltimore, MD 21287, United States

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjgnet.com/1948-9366/editorialboard.htm>

EDITORIAL OFFICE

Xiu-Xia Song, Director

Fang-Fang Ji, Vice Director

World Journal of Gastrointestinal Surgery
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLICATION DATE

September 27, 2016

COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

Update on medical and surgical options for patients with acute severe ulcerative colitis: What is new?

Rachel E Andrew, Evangelos Messaris

Rachel E Andrew, Evangelos Messaris, Department of Surgery, College of Medicine, the Pennsylvania State University, Hershey, PA 17033-0850, United States

Author contributions: Andrew RE acquired and analyzed the data, and drafted the manuscript; Andrew RE and Messaris E designed the study, interpreted the data and critically revised the manuscript for important intellectual content; Messaris E supervised the study.

Conflict-of-interest statement: We have no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Rachel E Andrew, MD, Department of Surgery, College of Medicine, the Pennsylvania State University, 500 University Drive, Hershey, PA 17033-0850, United States. randrew@hmc.psu.edu
Telephone: +1-717-5315164
Fax: +1-717-5310646

Received: March 29, 2016
Peer-review started: April 5, 2016
First decision: May 23, 2016
Revised: July 14, 2016
Accepted: July 29, 2016
Article in press: August 1, 2016
Published online: September 27, 2016

Abstract

Acute severe ulcerative colitis (UC) is a highly morbid condition that requires both medical and surgical management

through the collaboration of gastroenterologists and colorectal surgeons. First line treatment for patients presenting with acute severe UC consists of intravenous steroids, but those who do not respond require escalation of therapy or emergent colectomy. The mortality of emergent colectomy has declined significantly in recent decades, but due to the morbidity of this procedure, second line agents such as cyclosporine and infliximab have been used as salvage therapy in an attempt to avoid emergent surgery. Unfortunately, protracted medical therapy has led to patients presenting for surgery in a poorer state of health leading to poorer post-operative outcomes. In this era of multiple medical modalities available in the treatment of acute severe UC, physicians must consider the advantages and disadvantages of prolonged medical therapy in an attempt to avoid surgery. Colectomy remains a mainstay in the treatment of severe ulcerative colitis not responsive to corticosteroids and rescue therapy, and timely referral for surgery allows for improved post-operative outcomes with lower risk of sepsis and improved patient survival. Options for reconstructive surgery include three-stage ileal pouch-anal anastomosis or a modified two-stage procedure that can be performed either open or laparoscopically. The numerous avenues of medical and surgical therapy have allowed for great advances in the treatment of patients with UC. In this era of options, it is important to maintain a global view, utilize biologic therapy when indicated, and then maintain an appropriate threshold for surgery. The purpose of this review is to summarize the growing number of medical and surgical options available in the treatment of acute, severe UC.

Key words: Acute severe ulcerative colitis; Colectomy; Corticosteroids; Infliximab; Cyclosporine; Ileal pouch-anal anastomosis

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The numerous avenues of medical and sur-

gical therapy have allowed for great advances in the treatment of patients with ulcerative colitis. In this era of options, it is important to maintain a global view, utilize corticosteroids and rescue therapy when indicated, and then maintain an appropriate threshold for surgery. Colectomy remains a viable and often life-saving treatment and should not be viewed as the "therapy of last resort".

Andrew RE, Messaris E. Update on medical and surgical options for patients with acute severe ulcerative colitis: What is new? *World J Gastrointest Surg* 2016; 8(9): 598-605 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/598.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.598>

INTRODUCTION

Acute severe ulcerative colitis (UC) is an exacerbation of a chronic condition characterized by inflammation of the colonic mucosa extending from the rectum proximally to varying portions of the large intestine. UC is a highly morbid condition that requires both medical and surgical management. Prior to the 1950's and the implementation of urgent colectomy and systemic steroids, mortality rates were as high as 70% in patients with severe UC^[1]. In recent years, mortality rates have dropped to less than 1% with the combination of medical therapy, rescue therapy, and timely total abdominal colectomy (TAC) when indicated^[2,3]. Despite the introduction of rescue therapies such as cyclosporine (calcineurin inhibitor) and infliximab [tumor necrosis factor (TNF) monoclonal antibody] in the treatment regimen of patients with severe UC, colectomy rates have remained stable (27%) for the past thirty years^[4].

Historically, severe UC has been defined as the passage of at least six daily bloody stools, along with any of the following signs of systemic disease: Erythrocyte sedimentation rate > 30 mm/h, temperature > 37.8 °C, pulse rate > 90/min and hemoglobin < 10.5 g/dL (true-love and witts criteria)^[5]. Lichtiger created a scoring system for severe UC based on frequency of stools, nocturnal diarrhea, blood in stool, fecal incontinence, and abdominal pain^[6]. These criteria play a significant role in the decision to escalate therapy or proceed to colectomy in patients with severe disease. Rates of TAC within the first five years of disease range from 9%-35%, even with medical therapy^[7]. With a growing number of options available to both gastroenterologists and surgeons in the management of UC, treatment is becoming more individualized and variable. The following review provides a description of current medical and surgical management of acute severe UC.

STANDARD MEDICAL THERAPY

Patients presenting with signs of acute severe UC

require immediate admission to the hospital. They must have regular monitoring of vital signs and urine output as well as a comprehensive laboratory workup. Initial tests on admission should include a comprehensive metabolic panel, pre-albumin, albumin, complete blood count, and inflammatory markers [erythrocyte sedimentation rate and C-reactive protein (CRP)]^[5]. A tuberculin skin test should also be performed on that admission in preparation for possible treatment with immunosuppressant or biologic agents. Abdominal imaging should be obtained to evaluate for colonic dilation (greater than 5.5 cm) on plain X-ray or computed tomography scan, and the patient should be monitored for fever, leukocytosis and other signs of systemic sepsis that accompany toxic megacolon^[8,9].

Stool cultures and a clostridium difficile assay must be obtained to exclude infectious pseudomembranous colitis, and the frequency and consistency of bowel movements should be recorded.

Patients should take nothing by mouth and should be fluid resuscitated to a goal of 0.5 mL/kg per hour of urine output. The administration of intravenous fluids and the correction of electrolyte imbalances prevent dehydration and worsening of colonic dysmotility and dilatation^[10]. All patients who are not bleeding should be given thromboembolic prophylaxis due to the increased risk of thrombosis in the setting of systemic inflammation. In addition, the patient should undergo flexible sigmoidoscopy to confirm the diagnosis of acute severe UC and to obtain biopsies to rule out cytomegalovirus colitis^[11].

Patients with acute severe UC require constant reassessment, with antibiotic administration in the setting of infection, total parenteral nutrition in the setting of malnutrition, and escalation of therapy to medication non-responders. Kedia *et al.*^[12] proposed an algorithm for reassessing patient steroid response at days 1, 3 and 4-7 in which incomplete responders and non-responders either advance to rescue therapy or proceed to colectomy. In this algorithm, the Oxford criteria (> 8 stools/d or > 3 stools/d with a CRP > 45 mg/L) are used to determine the need for escalation of therapy^[13]. With careful attention to the patient's physical condition and severity of illness, the appropriate medical or surgical therapy can be selected to target the individual's ever-changing disease (Figure 1).

CORTICOSTEROIDS

Corticosteroids were introduced in the management of UC in the 1950's, though the first clinical trial proving their efficacy was not published until the 1970's^[5,14]. For the past 40 years, intravenous corticosteroids (methylprednisolone 60 mg/d or hydrocortisone 100 mg/8 h) for a 7-10 d course have been a cornerstone in the treatment of acute severe UC^[4,14]. A large review and meta-analysis reported the response to IV steroids to be 67% with short term colectomy rate of 29%^[4].

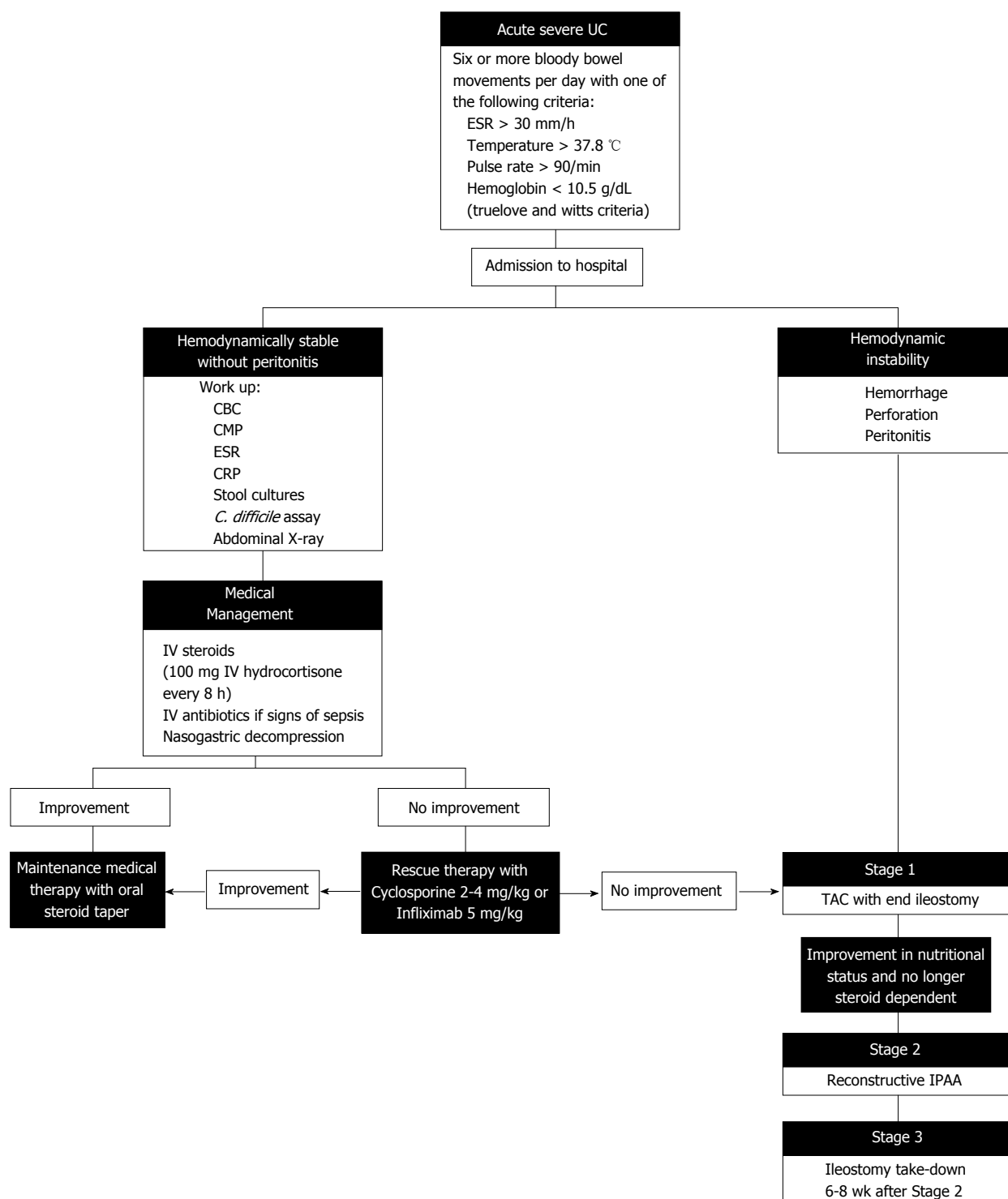


Figure 1 Algorithm for treatment of acute severe ulcerative colitis. UC: Ulcerative colitis; TAC: Total abdominal colectomy; IPAA: Ileal pouch-anal anastomosis; CBC: Complete blood count; CMP: Comprehensive metabolic panel; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

MEDICAL RESCUE THERAPY

Rescue therapies made their first appearance in the medical management of UC in the 1990's with the introduction of cyclosporine. Infliximab followed soon after as an alternative therapy with a different side-effect profile that could also serve as a salvage therapy in the setting of UC refractory to corticosteroids.

Cyclosporine (2-4 mg/kg) has been shown to induce

remission in 60%-80% of patients with acute severe colitis, but colectomy rates at four months remain close to 50% unless the patient is successfully bridged to maintenance therapy^[6,15,16]. The role of infliximab in the treatment of non-acute, moderate-to-severe UC has been reported in the Active Ulcerative Colitis Trials 1 and 2, with response rates between 61% and 69%^[17]. Infliximab (5 mg/kg) has also been shown to significantly decrease rate of colectomy at three months for patients with severe to

moderate attacks of UC^[18]. In an Italian trial by Kohn *et al.*^[19] there was an 85% response rate to infliximab with no colectomy in the 2 mo following hospital admission for acute severe UC and 67% at 23 mo. Multiple studies have compared infliximab and cyclosporine as rescue therapy for acute severe UC with no significant difference between the two therapies. Colectomy rates were similar at three and twelve months between patients receiving infliximab (31% and 41%) and cyclosporine (30% and 44%)^[20,21]. A recent systematic review and meta-analysis compared infliximab and cyclosporine as rescue therapy and found no significant difference in 3 or 12 mo colectomy rates among three randomized trials but reported significantly increased response to treatment and lower 12 mo colectomy rate among 12 non-randomized studies^[22].

While immunosuppressant and biologic agents have become established means of treating severe UC, there is conflicting evidence on the use of sequential therapy. Reports of the use of infliximab after failing steroids and cyclosporine have shown a 30% colectomy rate^[23]. A review of 10 studies in which rescue therapies were used sequentially for treatment of acute severe UC demonstrated colectomy rates of 28% at 3 mo and 42% at 12 mo with a 23% rate of adverse events—lower than previously reported in the literature^[24]. At this time, the selection of a rescue therapy agent, cyclosporine vs infliximab vs one agent following the other, is based primarily on physician comfort and experience, along with patient tolerance of side effects and susceptibility to infection.

IMMUNOMODULATORS

Although not currently the standard of care, vedolizumab, an integrin antibody, has been shown to induce steroid-free remission in approximately one third of UC patients who have failed anti-TNF therapy^[25]. Further investigation is required before recommendations can be made for its use in the treatment of acute severe UC.

Other agents such as thiopurines and methotrexate play a role in maintenance therapy and steroid dose reduction, but these drugs have shown no significant success as induction therapy to achieve remission in patients with active UC^[26,27].

ANTIBIOTICS

The role of antibiotics in the treatment of acute severe UC remains limited because even in severe UC there is no proven therapeutic benefit to oral or intravenous metronidazole, tobramycin, ciprofloxacin or vancomycin^[28–30]. Only in the setting of active infection or for pre-operative antibiotic prophylaxis do 2012 ECCO guidelines recommend that antibiotics be administered^[31].

SURGICAL THERAPY

Although tremendous advances have been made in the

medical treatment of UC, colectomy remains a cornerstone in the management of this disease. Overall, the rates of colectomy have not significantly changed since the addition of rescue therapies to the armamentarium of gastroenterologists. Predictors of the need for second-line treatment or colectomy are numerous, but several variables, including severity of disease, stool frequency, CRP, hypoalbuminemia (< 3 mg/dL), and radiographic evidence of colonic dilation (> 5.5 cm), all can be used in early identification of the need for escalation of therapy^[32–34]. A more recent scoring system also includes the need for blood transfusions or parenteral nutrition as predictors of need for colectomy^[35].

COLECTOMY AFTER MEDICAL RESCUE THERAPY

Due to the growing number of medical therapies for severe UC, patients are being referred for colectomy later after multiple attempts at medical salvage. These patients present in a poorer state of health, malnourished and anemic, and the delay is not without consequences.

Patients who undergo an operation after receiving high dose steroids or who are malnourished often have increased surgical complications^[36]. Post-operative complications include anastomotic leak, stricture, fistulae, and bowel obstruction. One study reported the rate of post-operative complications to be over three times higher, with the rate of sepsis being 13 times higher, in patients undergoing three-stage ileal pouch-anal anastomosis (IPAA) after treatment with infliximab^[37]. Similarly, significantly higher rates of major complications were found in patients undergoing longer duration of medical therapy (> 8 d) in a group of 80 patients with severe UC followed over the course of 7 years^[13].

The importance of continuous reassessment of the need for surgery is emphasized due to the mortality benefits of a well-timed or elective operation; mortality rates three years after elective colectomy (3.7%) are significantly lower than after admission without surgery (13.6%) or with emergent surgery (13.2%) in patients with acute severe UC^[38].

STAGED APPROACH

Surgical management of UC in the setting of failed medical therapy involves the performance of a TAC with an optional IPAA in two or three stages^[3]. In a three-stage approach, the initial operation involves a subtotal or TAC with creation of an end ileostomy. The stapled or hand-sewn rectosigmoid stump can be sutured as a mucous fistula to the distal aspect of the abdominal wall incision, may be closed and sutured to the subcutaneous tissue, or may be left unattached in the pelvis. The primary reason for creation of a mucous fistula or placement of the long rectal stump in the subcutaneous tissue is to avoid rectal stump breakdown and leakage with subsequent pelvic sepsis, especially in cases of severe

inflammation and thickening of tissue^[39]. The drawback to a mucous fistula lies in patient dissatisfaction that may occur with persistent discharge during the long-term recovery period^[40]. The manner in which the rectosigmoid is closed depends mainly upon patient anatomy and surgeon preference, but transanal rectal decompression is commonly performed following all techniques^[3]. TAC with end ileostomy as the first stage allows for immediate diversion of the fecal stream, avoids the dangers of a pelvic dissection or anastomosis in a critically ill patient, and allows for preservation of the rectum with the possible diagnosis of Crohn's colitis rather than UC.

The second stage of the procedure involves pouch formation with diverting ileostomy. Restorative procto-colectomy with IPAA is an elective operation performed in the absence of toxicity or severe malnutrition. Although proximal diversion does not prevent pelvic sepsis in the setting of IPAA, diverting ileostomy has been shown to lessen complications related to anastomotic leakage^[41,42]. The procedure can be technically challenging and involves identification of the rectal stump with full mobilization to the level of the levator ani muscles, proctectomy, and construction of a J-shaped pouch through a side-to-side anastomosis of the distal 40 cm of terminal ileum^[43]. Although several pouch designs have been promoted over the years, including the S-pouch and the W-pouch, the J-pouch has endured due to its relatively simple construction and equivalent or superior outcomes to other designs^[43,44]. The IPAA may be stapled or hand-sewn but fewer complications and better long-term quality of life have been reported in patients undergoing stapled anastomosis^[45].

The third stage of the procedure involves takedown of the diverting ileostomy and reestablishment of intestinal continuity. This final step should only be performed after water-soluble contrast enema has demonstrated patency and anastomotic integrity of the pouch.

In rare cases (5%), patients present with rectal sparing disease, and TAC with end ileostomy remains the first step to patient recovery^[46]. Only in these specific cases has ileorectal anastomosis as an alternative to pouch formation been described for reconstruction of the gastrointestinal tract^[47].

Although colectomy and pouch formation may be and are routinely performed as one procedure, this operation is reserved for UC patients who are healthy, well-nourished, off steroids and not experiencing an acute flare^[41]. Performing a three stage procedure allows for healthier, better nourished patients at the time of surgery^[48]. Some centers have attempted to abbreviate the hospital course of acute severe UC patients by performing a modified two-stage procedure (colectomy followed by IPAA and ileostomy takedown). Zittan *et al*^[49] demonstrated significantly lower rates of anastomotic leak (4.6% vs 15.7%) when comparing modified 2-stage IPAA to the traditional 2-stage procedure (colectomy with pouch formation followed by ileostomy takedown). Swenson *et al*^[50] demonstrated equivalent

patient outcomes with significantly lower hospital cost in patients with resolved severe colitis after colectomy who underwent a modified two-stage IPAA vs a three-stage procedure. The cost of medical therapy is not only affected by the operation performed but also by the timing of the procedure. In a comparison of patients with severe UC undergoing early colectomy with IPAA vs standard medical therapy, Park *et al*^[51] reported a cost analysis showing a \$90000 increase in cost to patients who received prolonged medical salvage therapy with very little improvement in quality of life.

ROLE OF LAPAROSCOPY

A laparoscopic approach to TAC in severe UC patients provides a reasonable alternative to the open approach and has been shown to be equally safe and feasible in comparison^[52]. While the laparoscopic approach has the advantage of reducing post-operative pain, time to stoma function, and overall hospital stay, it also leads to longer operative time and may be more technically demanding for the surgeon^[53,54].

LONG-TERM OUTCOMES OF IPAA

Although the ileal pouch does allow many patients to have a more normal life-style and defecation pattern, the procedure is not without enduring consequences. A recent study from the Cleveland Clinic published long-term outcomes of 74 patients who underwent IPAA and were followed over a 20-year period. Pouch-specific complications included pouchitis (45%), stricture (16%), fistula (30%), obstruction (20%), and change of diagnosis to Crohn's (28%). Long-term consequences of the procedure also included frequent stooling requiring anti-diarrheal medication (44%) and difficulty conceiving (25% and all women)^[44]. Pouch failure rates at 10 and 20 years have been reported to be 9% and 14%, although a 2016 study reported a failure rate of 2.4%, indicating that pouch outcomes may be improving^[44,55,56]. The three stage approach with proximal diversion may be associated with better outcomes as it reduces the impact that complications such as pelvic sepsis or anastomotic leak have on the ultimate quality of the pouch^[41].

While a substantial number of UC patients do elect to undergo IPAA after TAC, this procedure is not mandatory, and many choose to forgo the pouch completely. A Swedish cohort study of over 2000 patients who underwent colectomy for inflammatory bowel disease showed that less than half (43%) of the patients underwent reconstructive surgery over a ten year period^[57]. A 2015 review of UC patients with an end ileostomy or IPAA demonstrated equivalent improvement in quality of life at 1 year with the majority of the benefit related to the control of disease symptoms^[58].

CONCLUSION

The optimal treatment algorithm in the management

of severe UC remains controversial. The purpose of this review is to summarize the current medical and surgical options available in the treatment of acute, severe UC.

First line treatment for patients presenting with acute severe UC consists of intravenous steroids, but those who do not respond require escalation of therapy or emergent colectomy. The mortality of emergent colectomy has declined significantly in recent decades, but due to the morbidity of this procedure, second line agents such as cyclosporine and infliximab have been used as rescue therapy in an attempt to avoid emergent surgery. In this era of multiple medical modalities available in the treatment of acute severe UC, it is imperative that physicians consider the advantages and disadvantages of prolonged medical therapy in an attempt to avoid surgery. Colectomy remains a mainstay in the treatment of severe ulcerative colitis not responsive to corticosteroids and rescue therapy, and timely referral for surgery allows for improved post-operative outcomes with lower risk of sepsis and improved patient survival.

Options for reconstructive surgery include three-stage IPAA or a modified two-stage procedure. The three-stage procedure offers the advantage of a healthier, well-nourished patient, but the two-stage procedure offers fewer in-hospital days and decreased overall cost.

The numerous avenues of medical and surgical therapy have allowed for great advances in the treatment of patients with UC. In this era of options, it is important to maintain a global view, utilize rescue therapy when indicated, and then maintain an appropriate threshold for surgery. Colectomy remains a viable and often life-saving treatment and should not be viewed as the “therapy of last resort”.

ACKNOWLEDGMENTS

We would like to acknowledge Lisa McCully, Projects Specialist, for her assistance in designing Figure 1.

REFERENCES

- Hardy TL, Bulmer E. Ulcerative Colitis: A Survey of Ninety-five Cases. *Br Med J* 1933; **2**: 812-815 [PMID: 20777868 DOI: 10.1136/bmj.2.3800.812]
- Dayan B, Turner D. Role of surgery in severe ulcerative colitis in the era of medical rescue therapy. *World J Gastroenterol* 2012; **18**: 3833-3838 [PMID: 22876035 DOI: 10.3748/wjg.v18.i29.3833]
- Brown SR, Haboubi N, Hampton J, George B, Travis SP. The management of acute severe colitis: ACPGBI position statement. *Colorectal Dis* 2008; **10** Suppl 3: 8-29 [PMID: 18954307 DOI: 10.1111/j.1463-1318.2008.01682.x]
- Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007; **5**: 103-110 [PMID: 17142106 DOI: 10.1016/j.cgh.2006.09.033]
- Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: 13260656 DOI: 10.1136/bmj.2.4947.1041]
- Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer N. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330**: 1841-1845 [PMID: 8196726 DOI: 10.1056/NEJM199406303302601]
- Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992; **103**: 1444-1451 [PMID: 1358741 DOI: 10.1016/0016-5085(92)91163-X]
- Trudel JL, Deschênes M, Mayrand S, Barkun AN. Toxic megacolon complicating pseudomembranous enterocolitis. *Dis Colon Rectum* 1995; **38**: 1033-1038 [PMID: 7555415 DOI: 10.1007/BF02133974]
- Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2016; **43**: 482-513 [PMID: 26725569 DOI: 10.1111/apt.13491]
- Gan SI, Beck PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. *Am J Gastroenterol* 2003; **98**: 2363-2371 [PMID: 14638335 DOI: 10.1111/j.1572-0241.2003.07696.x]
- Criscuolo V, Casà A, Orlando A, Pecoraro G, Oliva L, Traina M, Rizzo A, Cottone M. Severe acute colitis associated with CMV: a prevalence study. *Dig Liver Dis* 2004; **36**: 818-820 [PMID: 15646428 DOI: 10.1016/j.dld.2004.05.013]
- Kedia S, Ahuja V, Tandon R. Management of acute severe ulcerative colitis. *World J Gastrointest Pathophysiol* 2014; **5**: 579-588 [PMID: 25401001 DOI: 10.4291/wjgp.v5.i4.579]
- Randall J, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg* 2010; **97**: 404-409 [PMID: 20101648 DOI: 10.1002/bjs.6874]
- Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974; **1**: 1067-1070 [PMID: 4135487]
- Cheifetz AS, Stern J, Garud S, Goldstein E, Malter L, Moss AC, Present DH. Cyclosporine is safe and effective in patients with severe ulcerative colitis. *J Clin Gastroenterol* 2011; **45**: 107-112 [PMID: 20679905 DOI: 10.1097/MCG.0b013e3181e883dd]
- Fornaro R, Caratto M, Barbruni G, Fornaro F, Salerno A, Giovannazzo D, Sticchi C, Caratto E. Surgical and medical treatment in patients with acute severe ulcerative colitis. *J Dig Dis* 2015; **16**: 558-567 [PMID: 26315728 DOI: 10.1111/1751-2980.12278]
- Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johans J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095 DOI: 10.1056/NEJMoa050516]
- Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilén M, Ström M, Danielsson A, Verbaan H, Hellström PM, Magnuson A, Curman B. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; **128**: 1805-1811 [PMID: 15940615 DOI: 10.1053/j.gastro.2005.03.003]
- Kohn A, Daperno M, Armuzzi A, Cappello M, Biancone L, Orlando A, Viscido A, Annese V, Riegler G, Meucci G, Marrolo M, Sostegni R, Gasbarrini A, Peralta S, Prantera C. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther* 2007; **26**: 747-756 [PMID: 17697208 DOI: 10.1111/j.1365-2036.2007.03415.x]
- Chang KH, Burke JP, Coffey JC. Infliximab versus cyclosporine as rescue therapy in acute severe steroid-refractory ulcerative colitis: a systematic review and meta-analysis. *Int J Colorectal Dis* 2013; **28**: 287-293 [PMID: 23114475 DOI: 10.1007/s00384-012-1602-8]
- Croft A, Walsh A, Doecke J, Cooley R, Howlett M, Radford-Smith G. Outcomes of salvage therapy for steroid-refractory acute severe ulcerative colitis: ciclosporin vs. infliximab. *Aliment Pharmacol Ther* 2013; **38**: 294-302 [PMID: 23786158 DOI: 10.1111/apt.12375]
- Narula N, Marshall JK, Colombel JF, Leontiadis GI, Williams JG, Muqtadir Z, Reinisch W. Systematic Review and Meta-Analysis: Infliximab or Cyclosporine as Rescue Therapy in Patients With Severe Ulcerative Colitis Refractory to Steroids. *Am J Gastroenterol* 2016; **111**: 477-491 [PMID: 26856754 DOI: 10.1038/ajg.2016.7]
- Chaparro M, Burgueño P, Iglesias E, Panés J, Muñoz F, Bastida G, Castro L, Jiménez C, Mendoza JL, Barreiro-de Acosta M, Senent SG, Gomollón F, Calvet X, García-Planella E, Gómez

- M, Hernández V, Hinojosa J, Mañosa M, Nyssen OP, Gisbert JP. Infliximab salvage therapy after failure of ciclosporin in corticosteroid-refractory ulcerative colitis: a multicentre study. *Aliment Pharmacol Ther* 2012; **35**: 275-283 [PMID: 22142227 DOI: 10.1111/j.1365-2036.2011.04934.x]
- 24 **Narula N**, Fine M, Colombel JF, Marshall JK, Reinisch W. Systematic Review: Sequential Rescue Therapy in Severe Ulcerative Colitis: Do the Benefits Outweigh the Risks? *Inflamm Bowel Dis* 2015; **21**: 1683-1694 [PMID: 25839775 DOI: 10.1097/MIB.0000000000000350]
- 25 **Amiot A**, Grimaud JC, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, Buisson A, Stefanescu C, Trang-Poisson C, Altwegg R, Marteau P, Vaysse T, Bourrier A, Nancey S, Laharie D, Allez M, Savoye G, Moreau J, Gagniere C, Vuitton L, Viennot S, Aubourg A, Pelletier AL, Bouguen G, Abitbol V, Bouhnik Y; Observatory on Efficacy and of Vedolizumab in Patients With Inflammatory Bowel Disease Study Group and the Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif. Effectiveness and Safety of Vedolizumab Induction Therapy for Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2016; Epub ahead of print [PMID: 26917043 DOI: 10.1016/j.cgh.2016.02.016]
- 26 **Khan HM**, Mehmood F, Khan N. Optimal management of steroid-dependent ulcerative colitis. *Clin Exp Gastroenterol* 2015; **8**: 293-302 [PMID: 26648749 DOI: 10.2147/CEG.S57248]
- 27 **Bressler B**, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, Panaccione R, Steinhart AH, Tse F, Feagan B. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology* 2015; **148**: 1035-1058.e3 [PMID: 25747596 DOI: 10.1053/j.gastro.2015.03.001]
- 28 **Chapman RW**, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. *Gut* 1986; **27**: 1210-1212 [PMID: 3536677]
- 29 **Nitzan O**, Elias M, Peretz A, Saliba W. Role of antibiotics for treatment of inflammatory bowel disease. *World J Gastroenterol* 2016; **22**: 1078-1087 [PMID: 26811648 DOI: 10.3748/wjg.v22.i3.1078]
- 30 **Khan KJ**, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, Talley NJ, Moayyedi P. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106**: 661-673 [PMID: 21407187 DOI: 10.1038/ajg.2011.72]
- 31 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]
- 32 **Ho GT**, Mowat C, Goddard CJ, Fennell JM, Shah NB, Prescott RJ, Satsangi J. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* 2004; **19**: 1079-1087 [PMID: 15142197 DOI: 10.1111/j.1365-2036.2004.01945.x]
- 33 **Travis SP**, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905-910 [PMID: 8984031 DOI: 10.1136/gut.38.6.905]
- 34 **Lindgren SC**, Flood LM, Kilander AF, Löfberg R, Persson TB, Sjö Dahl RI. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998; **10**: 831-835 [PMID: 9831403]
- 35 **Ananthakrishnan AN**, McGinley EL, Binion DG, Saeian K. Simple score to identify colectomy risk in ulcerative colitis hospitalizations. *Inflamm Bowel Dis* 2010; **16**: 1532-1540 [PMID: 20091926 DOI: 10.1002/ibd.21225]
- 36 **Markel TA**, Lou DC, Pfefferkorn M, Scherer LR, West K, Rouse T, Engum S, Ladd A, Rescorla FJ, Billmire DF. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. *Surgery* 2008; **144**: 540-545; discussion 545-547 [PMID: 18847637 DOI: 10.1016/j.surg.2008.07.005]
- 37 **Mor IJ**, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008; **51**: 1202-1207; discussion 1202-1210 [PMID: 18536964 DOI: 10.1007/s10350-008-9364-7]
- 38 **Roberts SE**, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. *BMJ* 2007; **335**: 1033 [PMID: 17977817 DOI: 10.1136/bmj.39345.714039.55]
- 39 **Pellino G**, Sciaudone G, Candilio G, Canonico S, Selvaggi F. Rectosigmoid stump washout as an alternative to permanent mucous fistula in patients undergoing subtotal colectomy for ulcerative colitis in emergency settings. *BMC Surg* 2012; **12** Suppl 1: S31 [PMID: 23173990 DOI: 10.1186/1471-2482-12-S1-S31]
- 40 **Brady RR**, Collier MH, Ho GT, Bartolo DC, Wilson RG, Dunlop MG. Outcomes of the rectal remnant following colectomy for ulcerative colitis. *Colorectal Dis* 2008; **10**: 144-150 [PMID: 17302914]
- 41 **Fazio VW**, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, Manilich E, Shen B, Martin ST. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013; **257**: 679-685 [PMID: 23299522 DOI: 10.1097/SLA.0b013e31827d99a2]
- 42 **Wong NY**, Eu KW. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. *Dis Colon Rectum* 2005; **48**: 2076-2079 [PMID: 16086220 DOI: 10.1007/s10350-005-0146-1]
- 43 **Sagar PM**, Taylor BA. Pelvic ileal reservoirs: the options. *Br J Surg* 1994; **81**: 325-332 [PMID: 8173895 DOI: 10.1002/bjs.1800810304]
- 44 **Shannon A**, Eng K, Kay M, Blanchard S, Wyllie R, Mahajan L, Worley S, Lavery I, Fazio V. Long-term follow up of ileal pouch anal anastomosis in a large cohort of pediatric and young adult patients with ulcerative colitis. *J Pediatr Surg* 2016; **51**: 1181-1186 [PMID: 26876089 DOI: 10.1016/j.jpedsurg.2015.12.012]
- 45 **Kirat HT**, Remzi FH, Kiran RP, Fazio VW. Comparison of outcomes after hand-sewn versus stapled ileal pouch-anal anastomosis in 3,109 patients. *Surgery* 2009; **146**: 723-729; discussion 729-730 [PMID: 19789032 DOI: 10.1016/j.surg.2009.06.041]
- 46 **Joo M**, Odze RD. Rectal sparing and skip lesions in ulcerative colitis: a comparative study of endoscopic and histologic findings in patients who underwent proctocolectomy. *Am J Surg Pathol* 2010; **34**: 689-696 [PMID: 20410806 DOI: 10.1097/PAS.0b013e3181db84cd]
- 47 **Scoglio D**, Ahmed Ali U, Fichera A. Surgical treatment of ulcerative colitis: ileorectal vs ileal pouch-anal anastomosis. *World J Gastroenterol* 2014; **20**: 13211-13218 [PMID: 25309058 DOI: 10.3748/wjg.v20.i37.13211]
- 48 **Bikhchandani J**, Polites SF, Wagie AE, Habermann EB, Cima RR. National trends of 3- versus 2-stage restorative proctocolectomy for chronic ulcerative colitis. *Dis Colon Rectum* 2015; **58**: 199-204 [PMID: 25585078 DOI: 10.1097/DCR.0000000000000282]
- 49 **Zittan E**, Wong-Chong N, Ma GW, McLeod RS, Silverberg MS, Cohen Z. Modified Two-stage Ileal Pouch-Anal Anastomosis Results in Lower Rate of Anastomotic Leak Compared with Traditional Two-stage Surgery for Ulcerative Colitis. *J Crohns Colitis* 2016; **10**: 766-772 [PMID: 26951468 DOI: 10.1093/ecco-jcc/jjw069]
- 50 **Swenson BR**, Hollenbeak CS, Poritz LS, Koltun WA. Modified two-stage ileal pouch-anal anastomosis: equivalent outcomes with less resource utilization. *Dis Colon Rectum* 2005; **48**: 256-261 [PMID: 15711857 DOI: 10.1007/s10350-004-0848-9]
- 51 **Park KT**, Tsai R, Perez F, Cipriano LE, Bass D, Garber AM. Cost-effectiveness of early colectomy with ileal pouch-anal anastomosis versus standard medical therapy in severe ulcerative colitis. *Ann Surg* 2012; **256**: 117-124 [PMID: 22270693 DOI: 10.1097/SLA.0b013e3182445321]

- 52 **Watanabe K**, Funayama Y, Fukushima K, Shibata C, Takahashi K, Sasaki I. Hand-assisted laparoscopic vs. open subtotal colectomy for severe ulcerative colitis. *Dis Colon Rectum* 2009; **52**: 640-645 [PMID: 19404068 DOI: 10.1007/DCR.0b013e31819d47b5]
- 53 **Messenger DE**, Mihailovic D, MacRae HM, O'Connor BI, Victor JC, McLeod RS. Subtotal colectomy in severe ulcerative and Crohn's colitis: what benefit does the laparoscopic approach confer? *Dis Colon Rectum* 2014; **57**: 1349-1357 [PMID: 25379999 DOI: 10.1097/DCR.0000000000000238]
- 54 **Gu J**, Stocchi L, Remzi FH, Kiran RP. Total abdominal colectomy for severe ulcerative colitis: does the laparoscopic approach really have benefit? *Surg Endosc* 2014; **28**: 617-625 [PMID: 24196546 DOI: 10.1007/s00464-013-3218-7]
- 55 **Meagher AP**, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch-anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. *Br J Surg* 1998; **85**: 800-803 [PMID: 9667712]
- 56 **Dafnis G**. Early and late surgical outcomes of ileal pouch-anal anastomosis within a defined population in Sweden. *Eur J Gastroenterol Hepatol* 2016; **28**: 842-849 [PMID: 26945126 DOI: 10.1097/MEG.0000000000000618]
- 57 **Nordenvall C**, Myrelid P, Ekblom A, Bottai M, Smedby KE, Olén O, Nilsson PJ. Probability, rate and timing of reconstructive surgery following colectomy for inflammatory bowel disease in Sweden: a population-based cohort study. *Colorectal Dis* 2015; **17**: 882-890 [PMID: 25885419 DOI: 10.1111/codi.12978]
- 58 **Murphy PB**, Khot Z, Vogt KN, Ott M, Dubois L. Quality of Life After Total Proctocolectomy With Ileostomy or IPAA: A Systematic Review. *Dis Colon Rectum* 2015; **58**: 899-908 [PMID: 26252853 DOI: 10.1097/DCR.0000000000000418]

P- Reviewer: Madhani MA, Matowicka-Karna J

S- Editor: Gong ZM **L- Editor:** A **E- Editor:** Li D



Role of surgery for colorectal cancer in the elderly

Antonio Biondi, Marco Vacante, Immacolata Ambrosino, Erika Cristaldi, Giuseppe Pietrapertosa, Francesco Basile

Antonio Biondi, Francesco Basile, Department of Surgery, Vittorio Emanuele Hospital, University of Catania, 95100 Catania, Italy

Marco Vacante, Erika Cristaldi, Department of Medical and Pediatric Sciences, University of Catania, 95100 Catania, Italy

Immacolata Ambrosino, Giuseppe Pietrapertosa, Community Hospital Service ULSS 20 Verona, 37122 Verona, Italy

Author contributions: All authors wrote and critically revised the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Antonio Biondi, MD, PhD, Associate Professor, Department of Surgery, Vittorio Emanuele Hospital, University of Catania, Via Plebiscito 628, 95100 Catania, Italy. abiondi@unict.it
Telephone: +39-95-7435373

Received: March 25, 2016

Peer-review started: March 25, 2016

First decision: May 23, 2016

Revised: June 15, 2016

Accepted: July 14, 2016

Article in press: July 18, 2016

Published online: September 27, 2016

Abstract

The prevalence of subjects with colorectal cancer is expected to grow in the next future decades and surgery represents the most successful treatment modality for these patients. Anyway, currently elderly subjects undergo less elective surgical procedures than younger patients mainly due to the high rates of postoperative morbidity and mortality. Some authors suggest extensive surgery, including multistage procedures, as carried out in younger patients while others promote less aggressive surgery. In older patients, laparoscopic-assisted colectomy showed a number of advantages compared to conventional open surgery that include lower stress, higher rate of independency after surgery, quicker return to prior activities and a decrease in costs. The recent advances in chemotherapy and the introduction of new surgical procedures such as the endoluminal stenting, suggest the need for a revisitation of surgical practice patterns and the role of palliative surgery, mainly for patients with advanced disease. In this article, we discuss the current role of surgery for elderly patients with colorectal cancer.

Key words: Laparoscopy; Colorectal cancer; Elderly; Comorbidities; Colorectal surgery

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for colorectal cancer. Many studies underlined that age is not a predictor of post operative complications in these patients. Therapeutic or palliative surgery should not be avoided in the elderly based exclusively on age.

Biondi A, Vacante M, Ambrosino I, Cristaldi E, Pietrapertosa G, Basile F. Role of surgery for colorectal cancer in the elderly. *World J Gastrointest Surg* 2016; 8(9): 606-613 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/606.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.606>

INTRODUCTION

Colorectal cancer (CRC) represents the third most commonly diagnosed cancer in developed countries, with almost 694000 deaths estimated to have occurred in 2012^[1]. The prevalence of elderly subjects with CRC is expected to grow in the next future decades due to the increase of age in the general population^[2]. In fact, CRC is infrequently diagnosed before age of 40, with a highest risk around age of 70.75% of CRC are identified in patients aged 65 years or older^[3]. In both Europe and United States approximately 50% of CRC patients are older than 70 years of age and in this age group CRC is the second most common cause of cancer death^[4,5]. Thus, age could be considered as a major risk factor for the development of this cancer^[6].

Many studies showed that surgical approach represents the most successful treatment modality for patients with CRC. Over the past years it has been observed an improvement in the survival of subjects with this cancer mainly due to a reduction in operative mortality and a raising in the resection rate^[7]. However, there is significant evidence that elderly subjects undergo less elective surgical procedures than younger patients^[8] mainly due to the high rates of postoperative morbidity and mortality^[9].

IMPACT OF AGE ON CRC SURGERY

There is a lack of consensus on the impact of age on postoperative outcome after major colorectal surgery. In fact, comorbidities are higher in elderly subjects thus leading to difficult decisions whether these patients are suitable for extensive bowel resection or not. A review of the literature published in the *Lancet* in 2000 pointed out that elderly patients are less likely to have curative surgery than younger patients^[8].

In 2008, the International Society of Geriatric Oncology (SIOG) created a task force to develop guidelines for the treatment of elderly patients with CRC^[10]. The task force confirmed the paucity of clinical trial data in the elderly and pointed out that treatment for elderly CRC patients should be analogous to those of younger patients.

A registry-based study carried out by Damhuis *et al*^[9] on 6457 patients with CRC, evaluated the influence of age and other variables on resection rates and operative risk. All subjects included in the study were enrolled from 1985 through 1992 in hospitals connected to the Rotterdam Cancer Registry. Data analysis showed that 87% of the patients underwent resection but resection

rates were lower for patients older than 89 years (67%) and for patients with rectal cancer (83%). Patients younger than 60 years had a postoperative mortality rate of 1% that constantly increased with age. Patients 80 years and older showed an operative risk of 10%. Multivariate analysis was conducted and pointed out that gender, age, cancer subsite and stage could be considered as independent prognostic factors. The authors concluded that chronological age alone should not be an exclusion criteria for performing surgery in elderly patients with CRC. Even in patients aged over 90 years, resections can be performed with acceptable risk.

Another study^[11] analysed the electronic records from the Rotterdam Cancer Registry for octogenarians and nonagenarians who underwent resection in the period 1987-2000. The results showed that for CRC, postoperative mortality rates increased from 8% in patients aged 80 to 84 years, to 13% in patients aged 85 to 89 years and to 20% in nonagenarians.

A systematic review of 28 independent studies and 34194 patients, carried out by the Colorectal Cancer Collaborative Group, analysed the results for different groups of patients aged 65-74 years, 75-84 years and 85+ years with those for patients aged < 65 years. Compared with younger subjects, elderly patients have an increased frequency of comorbid conditions, are more likely to present with later-stage disease and undergo emergency surgery^[8]. Moreover, many studies focused on the role of adjuvant chemotherapy, demonstrating that elderly are less likely to be recommended or to receive adjuvant treatment^[12].

COMORBIDITIES AND COMPLICATIONS

Traditionally, contraindications for major surgery in elderly patients include a poor functional status, associated comorbidities and impaired cognition^[13]. Anyway, in the last 30 years elderly patients with CRC took advantage of healthcare progress and a retrospective trend analysis showed a reduction of palliative procedures and a decline in operative mortality for these patients^[14].

Most elderly patients with CRC have significant comorbidities such as cardiovascular and pulmonary diseases. Such diseases increase the operative risk and the risk of postoperative morbidity and mortality^[15,16]. A study by Hermans *et al*^[17] evaluated the impact of comorbidities on the outcome of colonic surgery in elderly patients with colon cancer.

Comorbid assessment tools provide helpful information on the impact of comorbidities at the initial diagnosis and prospective outcome of CRC patients due to their prognostic capacity on survival. According to the classification of Charlson *et al*^[18], the evaluated comorbidities included previous malignancies, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, hypertension, diabetes, and others (rheumatoid arthritis, hyperthyroidism, hypothyroidism, and scleroderma). Compared to younger

age, elderly subjects presented with more cardiovascular pathology and dementia and with more than one type of the previously described comorbidities. The authors concluded that the type and number of co-morbidities influence post-operative mortality and morbidity. Complications were seen in 24% of younger patients vs 50% of elderly patients. No difference was observed as regards major complications (e.g., anastomotic leakage, fascia dehiscence, or intra-abdominal abscesses). In the elderly group there was a high incidence of delirium, pneumonia, wound infections, and minor complications such as urinary tract infection, and electrolyte alterations. Other factors that may cause poor outcome of surgery in the elderly include delayed presentation and advanced stage of the disease^[19,20].

As regards preoperative factors that could influence the choice of treatment, Marventano *et al.*^[19] proposed a modified version of the Charlson comorbidity index (CCI) that was specifically developed for colorectal cancer patients. This version of CCI emphasized the importance of specific conditions to better predict the survival of the patients. Particularly, the inclusion of 6-mo weight loss $\geq 20\%$, smoking > 20 cigarettes/d, underweight condition, and cardiac arrhythmias to the other comorbid conditions tested in the CCI showed a better predictive value compared with the original CCI and other comorbidity indices (e.g., the Elixhauser method, the National Institute on Aging and National Cancer Institute comorbidity index, and the Adult Comorbidity Evaluation-27). Noteworthy, the Authors found that only moderate or severe renal disease and diagnosis of AIDS were independently associated with higher risk of death^[19].

An analysis of 31574 patients in the surveillance, epidemiology and end results-medicare database for patients diagnosed with colon cancer between 1992 and 2005 was conducted to describe patterns of surgery in patients aged > 80 years and examine outcomes with and without colectomy. The Authors demonstrated that 80% of the "oldest old" patients with colon cancer in the United States are undergoing surgical resection^[21]. In this study, 46% of subjects were diagnosed during an urgent or emergent hospital admission, with decreased 1-year overall survival (70% vs 86% for patients diagnosed during an elective admission). Older age, black race, more hospital admission, use of home oxygen, use of wheelchair, frailty and dementia were most predictive of nonoperative management. The 1-year overall survival rate for both operative and nonoperative patients was lower than the colon cancer-specific survival rate (operative patients: 78% vs 89%; nonoperative patients: 58% vs 78%)^[21].

A study by Kahn *et al.*^[22] showed that older age is not independently associated with complications after surgery for colorectal cancer. The Authors underlined the importance of clinical status and American Society of Anesthesiologists (ASA) class in patients' selection rather than age.

THERAPEUTIC OPTIONS FOR CRC IN THE ELDERLY

Different approaches to treat elderly subjects with CRC have been proposed over the past years. Some authors endorse extensive surgery, including multistage procedures, as carried out in younger patients^[23,24], while others promote less aggressive surgery^[25,26].

Most subjects with stage I or II CRC are treated by surgery, even if some patients with stage II could benefit from adjuvant therapy^[27,28]. Surgery followed by adjuvant chemotherapy is the standard treatment for stage III CRC. Subjects with metastases could benefit from chemotherapy alone or combined with targeted therapy. At this stage, surgery is indicated in selected patients. The treatment for stage IV CRC includes surgery and preoperative or postoperative, radiotherapy and/or chemotherapy.

Different factors could influence surgical outcomes in stage IV CRC, including the presence of liver metastases^[29,30] and cardiovascular disease^[31], the degree of peritoneal involvement and primary cancer resection^[32], the tumor differentiation, and age older than 75^[33].

There is still uncertainty about the effective benefit of surgery directed toward removal of the primary tumor for the management of asymptomatic patients with stage IV CRC and unresectable metastases. Palliative surgery is indicated for most patients with bowel obstruction or uncontrollable bleeding^[34].

Guidelines from the National Comprehensive Cancer Network recommend surgical treatment in stage IV CRC only in symptomatic patients at risk of obstruction, or with metastases suitable for potentially curative resection^[35].

A study by Temple *et al.*^[34] evaluated surgical practice patterns for patients over 65 years of age with stage IV CRC in a United States population-based cohort. They observed that 72% of patients received primary-cancer-directed surgery (CDS) with a 30-d postoperative mortality of 10%. CDS was less performed on patients with left-sided or rectal lesions, subjects older than 75 years, blacks, and those of lower socioeconomic status; but even among those older than age 75, the CDS rate was 69%. Chemotherapy was administered to 47% of patients that underwent CDS vs 31% of patients who did not. The resection of metastases was performed only on 3.9% of patients at any point from diagnosis to death^[34].

There is evidence that subjects with stage IV CRC could tolerate chemotherapy without requiring surgery to remove the primary tumor. In fact, a study by Tebbutt *et al.*^[36] showed that there were no differences in gastrointestinal complications (e.g., fistulas, peritonitis, obstruction) in patients who did not undergo CDS compared to those who had CDS^[36]. The recent advances in chemotherapy and the introduction of new surgical procedures (e.g., endoluminal stenting) suggest the need for a revisitation of surgical practice patterns and the role of palliative surgery for IV stage CRC patients.

Many studies underlined the importance of laparoscopic assisted colectomy (LAC) for the treatment of CRC. However the majority of them were conducted on patients younger than 65 years. In general, LAC showed a number of advantages compared to conventional open surgery that include lower stress, higher rate of independency after surgery, quicker return to prior activities and a decrease in costs^[37,38].

There are many issues related to the limited number of LAC carried out on elderly subjects requiring colectomy: First of all, the high number of comorbidities; second, the longer operative times; and third, the paucity of scientific literature assessing risks and benefits of this procedure in the elderly. A review of the literature carried out by Mutch^[37] identified 18 studies on LAC in the elderly. There is significant evidence that LAC could be performed in the elderly population safely and without significant increase in morbidity and mortality^[38].

A study by Vara-Thorbeck *et al.*^[39] represents the first report of LAC in older patients. The study was conducted on 18 patients that underwent LAC for CRC. Eleven subjects were older than 70 years. None of the cases were converted to open laparotomy, and the mortality was null. The results showed that LAC could be performed safely on both older and younger patients while maintaining the same principles of surgical technique as open colectomy. A number of more recent studies confirmed that laparoscopy-assisted colectomy in the elderly can be performed with no difference in morbidity or length of hospital stay compared with open surgery^[40-44]. Vignali *et al.*^[45], compared the outcomes of open colectomy vs LAC in a population of octogenarians. They observed that the patients undergoing LAC had a shorter hospital stay (LAC 9.8 d vs open 12.9 d), reduced morbidity (LAC 21% vs open 31%), and higher rate of independence at discharge (LAC 98% vs open 82%), thus confirming that the benefits of LAC are maintained with advancing age.

A study by Bardram *et al.*^[46] analyzed the outcomes of laparoscopy combined with a perioperative multimodal rehabilitation protocol in 50 patients of median age 81 years. After LAC, patients were treated with epidural local anaesthesia for 2 d, early mobilization and oral nutrition, with a significant improvement in recovery.

O'Connell *et al.*^[47] pointed out that in frail elderly with limited life expectancy, the benefits of cancer surgery are frequently unclear, and surgical resection of tumors is less performed as the patient ages.

A study by Finlayson *et al.*^[48] aimed to determine functional status and mortality rates after colon cancer surgery in older nursing home residents. They conclude that even when not curative, surgery for CRC may be an effective palliative procedure. Less invasive treatments, such as endoscopic treatment or embolization of bleeding tumors or the use of endoluminal stents for large bowel obstruction, may represent an alternative to surgery for individuals with limited life expectancy.

The international SIOG expert recommendations, according to the available evidence on CRC in the elderly, suggested that emergency surgery should be avoided

when possible; the use of colorectal stents should be taken into account to improve patient nutrition thus facilitating elective surgery 1-2 wk after the patient has presented as an emergency; the pathway of choice should be elective surgery with a prospective analysis of the perioperative variables and careful treatment; possible curative resection of liver metastases should be performed in healthy elderly subjects receiving a careful preoperative assessment and a high quality postoperative care^[10].

As regards rectal cancer, analysis of 991 treatments, in the 838 elderly rectal cancer patients from the Cote d'Or and Calvados tumor registries study^[49], showed 54% of patients to undergo curative resection, 7% to undergo palliative resection, 12% to undergo by-pass laparotomy, 27% to undergo no surgery, 17% to receive radiotherapy and 2% to receive chemotherapy. These data highlighted a low use of radiotherapy either combined with surgery or alone, while chemotherapy was almost never administered. Both surgery and radiotherapy are important for controlling local recurrence and therefore local failure rates. Recently the use of the surgical technique total mesorectal excision^[50] has contributed to a reduction in pelvic recurrences. A study by Kim *et al.*^[51] assessed the long-term oncological and functional outcomes of intersphincteric resection for T2 and T3 low rectal cancer. The authors observed a 5-year overall survival rates of 95.8% for T2 and of 94.7% for T3. The 5-year recurrence-free survival rates were 87.5% for T2 and 86.8% for T3 (Table 1). Radiotherapy has been shown to impact significantly on survival in resectable tumors^[52] and is critical for the management of patients with all stages of rectal tumors.

CONCLUSION

In general, there are age-related disparities in colon cancer treatment, with older patients being less likely to receive recommended therapy. According to the SIOG guidelines, elderly subjects should receive screening and earlier diagnosis; the management of CRC should be more aggressive and closer to that received by younger patients; the treatment should be the most intensive and appropriate according to the biological age and the presence of comorbidities^[10]. Many studies pointed out that age is not a predictor of post operative complications in patients with CRC^[53-56]. Age itself should not be considered as a risk factor for the development of complications in patients undergoing surgery for CRC. Thus, therapeutic or palliative surgery based solely on age should not be avoided in these patients. In the future, the surgical assessment of CRC in the elderly should take into account a multidisciplinary process before choosing the best possible therapy for each patient. There will be the need for services specialized in the care of at-risk older patients, rehabilitation and palliative care consultation. An appropriate management should also include the functional status, the grade of frailty, the life expectancy and also patient's requests.

Table 1 Postoperative mortality, resection rates, comorbidities, survival rate and independent prognostic factors reported in different studies on colorectal surgery in the elderly

Ref.	Year	No. of patients	Postoperative mortality	Resection rates	Comorbidities	Survival rate	Independent prognostic factors
Damhuis <i>et al.</i> ^[9]	1996	6457	1% for patients < 60 yr and steadily increased with age. The operative risk was 10% for patients > 80 yr	87% of the patients underwent resection. 67% for patients > 89 yr and 83% for patients with rectal cancer	-	-	Gender, age, subsite and stage
Damhuis <i>et al.</i> ^[11]	2005	2765	Increased from 8% for the age group 80-84 to 13% for those 85-89 to 20% in nonagenarian	-	-	-	-
Hermans <i>et al.</i> ^[17]	2010	207	In-hospital mortality was 16% in the elderly and 5% in the younger group ($P < 0.01$)	No differences between < 75 yr and > 75 yr: ileocecal resection (2% vs 4%); hemicolectomy right (42% vs 49%); transverse resection (1% vs 3%); hemicolectomy left (15% vs 8%); sigmoid resection (26% vs 22%); anterior resection (10% vs 9%); subtotal colectomy (3% vs 1%); double resection (1% vs 4%)	More co-morbidities > 75 yr, especially cardiovascular pathology ($P < 0.01$) and dementia ($P < 0.01$). more than one type of comorbidity according to the Charlson classification ($P < 0.05$)	5-yr survival rate in < 75 yr was 62% compared with 36% in the elderly ($P < 0.05$)	-
Neuman <i>et al.</i> ^[21]	2013	31574	30-d mortality rate of 10% after urgent/emergent admission	-	Hypertension, peripheral vascular disease, and chronic pulmonary disease were found to be associated with improved overall and cancer-specific survival	The 1-yr overall survival rate was lower than the colon cancer-specific survival rate (operative patients: 78% vs 89%, non-operative patients: 56% vs 76%)	Older age, black race, more hospital admissions, use of home oxygen, use of a wheelchair, being frail, and having dementia
Irvin ^[23]	1988	306	The surgical mortality rates for patients > 70 yr were 6% overall, 4% after elective operations, and 16% after emergency surgery; the corresponding mortality rates for patients < 70 yr were 3%, 1%, and 20%	-	-	Crude actuarial 5-yr survival curves showed an increased death rate for patients > 70 yr after 18 mo and a significantly lower 5-yr survival ($P < 0.05$) but the age-corrected survival curves for the two groups were not significantly different	-
Temple <i>et al.</i> ^[34]	2004	9011	The 30-d postoperative mortality was 10%. The 30-d surgical mortality was significantly greater in the no primary cancer-directed surgery (CDS) group among patients who underwent a surgical procedure, when compared with the primary CDS group (26% vs 9%, $P = 0.001$)	The rates of CDS declined with age: 76% of 65 to 69-yr-old patients received primary CDS, whereas the rate declined to 62% of patients age ≥ 85 yr	-	The overall median survival for the entire cohort was 7 mo. There were differences in survival between patients treated with CDS and no CDS exist (median, 10 mo vs 3 mo, respectively), but data are not reliably because of patient selection in the non-randomized setting	Left-sided or rectal lesions, age > 75 yr, blacks, marital status and lower socioeconomic status
Vallribera Valls <i>et al.</i> ^[42]	2014	277: Laparoscopic group; 268: Open group	Open surgery group showed a higher mortality (6.7% vs 3.2%, $P = 0.034$). Mortality was significantly inferior in laparoscopy group in younger patients (< 75 yr, 0% vs 3%, $P = 0.038$)	-	Open surgery group showed a higher overall morbidity rate (37.3 vs 21.6%, $P = 0.001$), medical complications (16.4% vs 10.5%, $P = 0.033$), surgical complications (23.5% vs 15.5%, $P = 0.034$), the	-	-

				overall morbidity rate difference between open and laparoscopy approach disappeared in the oldest group (≥ 85 yrs old). Surgical site infections rate was inferior for patients < 75 yr old in laparoscopy group compared with open					
Vignali <i>et al</i> ^[45]	2005	61: Laparoscopic colectomy; 61: Open colectomy	Overall mortality rate was 2.4%. The morbidity rate was 21.5% in the laparoscopy group and 31.1% in the open group ($P = 0.30$)	-	-	-	-	Overall 3-yr survival rates were 45.2% for colon cancer and 46.2% for rectal cancer. Overall 5-yr survival rates were 40.9% and 37.3% respectively	Age, gender, period of diagnosis, treatment. A second multivariate analysis restricted to patients resected for cure and alive after the first month of follow-up showed that age between 85 and 89 was no longer a significant factor of survival
Bouvier <i>et al</i> ^[46]	2005	1571 with colon cancer; 838 with rectal cancer	During the study period from 8.7% to 9.5% for colon and from 16.3% to 5.6% for rectum	-	69% in colon cancer; 54% in rectal cancer	-	-	Overall 3-yr survival rates were 45.2% for colon cancer and 46.2% for rectal cancer. Overall 5-yr survival rates were 40.9% and 37.3% respectively	Age, gender, period of diagnosis, treatment. A second multivariate analysis restricted to patients resected for cure and alive after the first month of follow-up showed that age between 85 and 89 was no longer a significant factor of survival
Heald <i>et al</i> ^[50]	1998	519 with rectal cancer	The operative mortality (30-d) was 3.3%	-	-	-	-	68% at 5 yr and 66% at 10 yr	-
Kim <i>et al</i> ^[51]	2016	62 with very low rectal cancer. Group I, $n = 24$, stage T2 Group II, $n = 38$, stage T3	No postoperative mortality in both groups	-	-	-	Temporary urinary retention (group I : 10 cases; Group II : 15 cases), postoperative paralytic ileus (group I : 2 cases; Group II : 3 cases), perineal abscess (group I : 1 case; Group II : 1 case), and anastomotic leakage (group I : 1 case; Group II : 1 case). Late complications, such as anastomotic stricture (group I : 6 cases; Group II : 10 cases), rectovaginal fistula (group I : 0 case; Group II : 1 case) after stoma closure	5-yr overall survival rates were 95.8% for group I and 94.7% for group II. The 5-yr recurrence-free survival rates were 87.5% for group I and 86.8% for group II	-
Schiffmann <i>et al</i> ^[54]	2008	517	30-d mortality was higher in the older age group (> 75 yr)	-	-	-	No differences in 30-d morbidity except in postoperative bleeding	-	-
Devon <i>et al</i> ^[55]	2009	898	The in-hospital mortality rate was 1% in the younger group (< 75 yr) compared with 4.2% in the older (> 75 yr) ($P = 0.002$)	-	-	-	-	The overall five-year survival was 68.7% and 57.3% in the younger and older groups, respectively, whereas colorectal cancer-specific five-year survival was not significantly different (74.0% vs 74.7%)	-
Paksoy <i>et al</i> ^[56]	1999	822	The postoperative (30 d) mortality was 3% in the younger group (< 65 yr) (20/565) and 7% in the older group (17/257) (difference not significant)	-	-	-	-	Five-year survival rates for older and younger patients were 33% and 45%, respectively ($P < 0.05$)	-

REFERENCES

- 1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
- 2 **Mäkelä JT**, Kiviniemi H, Laitinen S. Survival after operations for colorectal cancer in patients aged 75 years or over. *Eur J Surg* 2000; **166**: 473-479 [PMID: 10890544 DOI: 10.1080/110241500750008790]
- 3 **Greenlee RT**, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001; **51**: 15-36 [PMID: 11577478 DOI: 10.3322/canjclin.51.1.15]
- 4 **Folprecht G**, Cunningham D, Ross P, Glimelius B, Di Costanzo F, Wils J, Scheithauer W, Rougier P, Aranda E, Hecker H, Köhne CH. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. *Ann Oncol* 2004; **15**: 1330-1338 [PMID: 15319237 DOI: 10.1093/annonc/mdh344]
- 5 **Grosso G**, Biondi A, Galvano F, Mistretta A, Marventano S, Buscemi S, Drago F, Basile F. Factors associated with colorectal cancer in the context of the Mediterranean diet: a case-control study. *Nutr Cancer* 2014; **66**: 558-565 [PMID: 24754383 DOI: 10.1080/01635581.2014.902975]
- 6 **de Rijke JM**, Schouten LJ, Hillen HF, Kiemeny LA, Coebergh JW, van den Brandt PA. Cancer in the very elderly Dutch population. *Cancer* 2000; **89**: 1121-1133 [PMID: 10964343 DOI: 10.1002/1097-0142(20000901)89]
- 7 **Marventano S**, Forjaz M, Grosso G, Mistretta A, Giorgianni G, Platania A, Gangi S, Basile F, Biondi A. Health related quality of life in colorectal cancer patients: state of the art. *BMC Surg* 2013; **13** Suppl 2: S15 [PMID: 24267735 DOI: 10.1186/1471-2482-13-S2-S15]
- 8 Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet* 2000; **356**: 968-974 [PMID: 11041397 DOI: 10.1016/S0140-6736(00)02713-6]
- 9 **Damhuis RA**, Wereldsma JC, Wiggers T. The influence of age on resection rates and postoperative mortality in 6457 patients with colorectal cancer. *Int J Colorectal Dis* 1996; **11**: 45-48 [PMID: 8919342]
- 10 **Papamichael D**, Audisio R, Horiot JC, Glimelius B, Sastre J, Mitry E, Van Cutsem E, Gosney M, Köhne CH, Aapro M. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. *Ann Oncol* 2009; **20**: 5-16 [PMID: 18922882 DOI: 10.1093/annonc/mdn532]
- 11 **Damhuis RA**, Meurs CJ, Meijer WS. Postoperative mortality after cancer surgery in octogenarians and nonagenarians: results from a series of 5,390 patients. *World J Surg Oncol* 2005; **3**: 71 [PMID: 16280074 DOI: 10.1186/1477-7819-3-71]
- 12 **Krzyzanowska MK**, Regan MM, Powell M, Earle CC, Weeks JC. Impact of patient age and comorbidity on surgeon versus oncologist preferences for adjuvant chemotherapy for stage III colon cancer. *J Am Coll Surg* 2009; **208**: 202-209 [PMID: 19228531 DOI: 10.1016/j.jamcollsurg.2008.10.016]
- 13 **Janssen-Heijnen ML**, Maas HA, Houterman S, Lemmens VE, Rutten HJ, Coebergh JW. Comorbidity in older surgical cancer patients: influence on patient care and outcome. *Eur J Cancer* 2007; **43**: 2179-2193 [PMID: 17681780 DOI: 10.1016/j.ejca.2007.06.008]
- 14 **Nascimbeni R**, Di Fabio F, Di Betta E, Salerni B. The changing impact of age on colorectal cancer surgery. A trend analysis. *Colorectal Dis* 2009; **11**: 13-18 [PMID: 18294264 DOI: 10.1111/j.1463-1318.2008.01491.x]
- 15 **De Marco MF**, Janssen-Heijnen ML, van der Heijden LH, Coebergh JW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *Eur J Cancer* 2000; **36**: 95-99 [PMID: 10741301 DOI: 10.1016/S0959-8049(99)00221-X]
- 16 **Grosso G**, Biondi A, Marventano S, Mistretta A, Calabrese G, Basile F. Major postoperative complications and survival for colon cancer elderly patients. *BMC Surg* 2012; **12** Suppl 1: S20 [PMID: 23173563 DOI: 10.1186/1471-2482-12-S1-S20]
- 17 **Hermans E**, van Schaik PM, Prins HA, Ernst MF, Dautzenberg PJ, Bosscha K. Outcome of colonic surgery in elderly patients with colon cancer. *J Oncol* 2010; **2010**: 865908 [PMID: 20628482 DOI: 10.1155/2010/865908]
- 18 **Charlson ME**, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-383 [PMID: 3558716 DOI: 10.1016/0021-9681(87)90171-8]
- 19 **Marventano S**, Grosso G, Mistretta A, Bogusz-Czerniewicz M, Ferranti R, Nolfo F, Giorgianni G, Rametta S, Drago F, Basile F, Biondi A. Evaluation of four comorbidity indices and Charlson comorbidity index adjustment for colorectal cancer patients. *Int J Colorectal Dis* 2014; **29**: 1159-1169 [PMID: 25064390 DOI: 10.1007/s00384-014-1972-1]
- 20 **Scott NA**, Jeacock J, Kingston RD. Risk factors in patients presenting as an emergency with colorectal cancer. *Br J Surg* 1995; **82**: 321-323 [PMID: 7795995 DOI: 10.1002/bjs.1800820311]
- 21 **Neuman HB**, O'Connor ES, Weiss J, Loconte NK, Greenblatt DY, Greenberg CC, Smith MA. Surgical treatment of colon cancer in patients aged 80 years and older: analysis of 31,574 patients in the SEER-Medicare database. *Cancer* 2013; **119**: 639-647 [PMID: 22893570 DOI: 10.1002/cncr.27765]
- 22 **Kahn KL**, Adams JL, Weeks JC, Chrischilles EA, Schrag D, Ayanian JZ, Kiefe CI, Ganz PA, Bhoopalam N, Potosky AL, Harrington DP, Fletcher RH. Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. *JAMA* 2010; **303**: 1037-1045 [PMID: 20233821 DOI: 10.1001/jama.2010.272]
- 23 **Irvin TT**. Prognosis of colorectal cancer in the elderly. *Br J Surg* 1988; **75**: 419-421 [PMID: 3390669 DOI: 10.1002/bjs.1800750508]
- 24 **Wobbes T**. Carcinoma of the colon and rectum in geriatric patients. *Age Ageing* 1985; **14**: 321-326 [PMID: 4072820 DOI: 10.1093/ageing/14.6.321]
- 25 **Greenburg AG**, Saik RP, Pridham D. Greenburg AG, Saik RP, Pridham D. Influence of age on mortality of colon surgery. *Am J Surg* 1985; **150**: 65-70 [PMID: 4014573 DOI: 10.1016/0002-9610(85)90011-X]
- 26 **Violi V**, Pietra N, Grattarola M, Sarli L, Choua O, Roncoroni L, Peracchia A. Curative surgery for colorectal cancer: long-term results and life expectancy in the elderly. *Dis Colon Rectum* 1998; **41**: 291-298 [PMID: 9514423 DOI: 10.1007/BF02237482]
- 27 **André T**, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350**: 2343-2351 [PMID: 15175436 DOI: 10.1056/NEJMoa032709]
- 28 **André T**, Tournigand C, Achille E, Tubiana-Mathieu N, Lledo G, Raoul Y, Carola E, Flesch M, Miron T, Boutan-Laroze A, Guérin Meyer V, Boaziz C, Maigre M, Ganem G, Mousseau M, Mounedji-Boudiaf L, de Gramont A. [Adjuvant treatment of colon cancer MOSAIC study's main results]. *Bull Cancer* 2006; **93** Suppl 1: S5-S9 [PMID: 16483940]
- 29 **Liu SK**, Church JM, Lavery IC, Fazio VW. Operation in patients with incurable colon cancer--is it worthwhile? *Dis Colon Rectum* 1997; **40**: 11-14 [PMID: 9102251 DOI: 10.1007/BF02055675]
- 30 **Biondi A**, Tropea A, Basile F. Clinical rescue evaluation in laparoscopic surgery for hepatic metastases by colorectal cancer. *Surg Laparosc Endosc Percutan Tech* 2010; **20**: 69-72 [PMID: 20393330 DOI: 10.1097/SLE.0b013e3181d83f02]
- 31 **Ruo L**, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. *J Am Coll Surg* 2003; **196**: 722-728 [PMID: 12742204 DOI: 10.1016/S1072-7515(03)00136-4]
- 32 **Rosen SA**, Buell JF, Yoshida A, Kazsuba S, Hurst R, Michelassi F, Millis JM, Posner MC. Initial presentation with stage IV colorectal cancer: how aggressive should we be? *Arch Surg* 2000; **135**: 530-534; discussion 534-535 [PMID: 10807276 DOI: 10.1001/archsurg.135.5.530]
- 33 **Joffe J**, Gordon PH. Palliative resection for colorectal carcinoma. *Dis Colon Rectum* 1981; **24**: 355-360 [PMID: 6167412 DOI: 10.1007/BF02603417]

- 34 **Temple LK**, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. *J Clin Oncol* 2004; **22**: 3475-3484 [PMID: 15337795 DOI: 10.1200/JCO.2004.10.218]
- 35 National Comprehensive Cancer Network: Clinical Practice Guidelines. Available from: URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
- 36 **Tebbutt NC**, Norman AR, Cunningham D, Hill ME, Tait D, Oates J, Livingston S, Andreyev J. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. *Gut* 2003; **52**: 568-573 [PMID: 12631671 DOI: 10.1136/gut.52.4.568]
- 37 **Mutch MG**. Laparoscopic colectomy in the elderly: when is too old? *Clin Colon Rectal Surg* 2006; **19**: 33-39 [PMID: 20011451 DOI: 10.1055/s-2006-939529]
- 38 **Biondi A**, Grosso G, Mistretta A, Marventano S, Toscano C, Drago F, Gangi S, Basile F. Laparoscopic vs. open approach for colorectal cancer: evolution over time of minimal invasive surgery. *BMC Surg* 2013; **13** Suppl 2: S12 [PMID: 24267544 DOI: 10.1186/1471-2482-13-S2-S12]
- 39 **Vara-Thorbeck C**, Garcia-Caballero M, Salvi M, Gutstein D, Toscano R, Gómez A, Vara-Thorbeck R. Indications and advantages of laparoscopy-assisted colon resection for carcinoma in elderly patients. *Surg Laparosc Endosc* 1994; **4**: 110-118 [PMID: 8180761]
- 40 **Hinoi T**, Kawaguchi Y, Hattori M, Okajima M, Ohdan H, Yamamoto S, Hasegawa H, Horie H, Murata K, Yamaguchi S, Sugihara K, Watanabe M. Laparoscopic versus open surgery for colorectal cancer in elderly patients: a multicenter matched case-control study. *Ann Surg Oncol* 2015; **22**: 2040-2050 [PMID: 25331007 DOI: 10.1245/s10434-014-4172-x]
- 41 **Kannan U**, Reddy VS, Mukerji AN, Parithivel VS, Shah AK, Gilchrist BF, Farkas DT. Laparoscopic vs open partial colectomy in elderly patients: Insights from the American College of Surgeons - National Surgical Quality Improvement Program database. *World J Gastroenterol* 2015; **21**: 12843-12850 [PMID: 26668508 DOI: 10.3748/wjg.v21.i45.12843]
- 42 **Vallribera Valls F**, Landi F, Espín Basany E, Sánchez García JL, Jiménez Gómez LM, Martí Gallostra M, Salgado Cruz L, Armengol Carrasco M. Laparoscopy-assisted versus open colectomy for treatment of colon cancer in the elderly: morbidity and mortality outcomes in 545 patients. *Surg Endosc* 2014; **28**: 3373-3378 [PMID: 24928231 DOI: 10.1007/s00464-014-3597-4]
- 43 **Delgado S**, Lacy AM, García Valdecasas JC, Balagué C, Pera M, Salvador L, Momblán D, Visa J. Could age be an indication for laparoscopic colectomy in colorectal cancer? *Surg Endosc* 2000; **14**: 22-26 [PMID: 10653230 DOI: 10.1007/s004649900004]
- 44 **Law WL**, Chu KW, Tung PH. Laparoscopic colorectal resection: a safe option for elderly patients. *J Am Coll Surg* 2002; **195**: 768-773 [PMID: 12495308 DOI: 10.1016/S1072-7515(02)01483-7]
- 45 **Vignali A**, Di Palo S, Tamburini A, Radaelli G, Orsenigo E, Staudacher C. Laparoscopic vs. open colectomies in octogenarians: a case-matched control study. *Dis Colon Rectum* 2005; **48**: 2070-2075 [PMID: 16086219 DOI: 10.1007/s10350-005-0147-0]
- 46 **Bardram L**, Funch-Jensen P, Kehlet H. Rapid rehabilitation in elderly patients after laparoscopic colonic resection. *Br J Surg* 2000; **87**: 1540-1545 [PMID: 11091243 DOI: 10.1046/j.1365-2168.2000.01559.x]
- 47 **O'Connell JB**, Maggard MA, Ko CY. Cancer-directed surgery for localized disease: decreased use in the elderly. *Ann Surg Oncol* 2004; **11**: 962-969 [PMID: 15525824 DOI: 10.1007/BF02524023]
- 48 **Finlayson E**, Zhao S, Varma MG. Outcomes after rectal cancer surgery in elderly nursing home residents. *Dis Colon Rectum* 2012; **55**: 1229-1235 [PMID: 23135580 DOI: 10.1097/DCR.0b013e318267bfe3]
- 49 **Bouvier AM**, Launoy G, Lepage C, Faivre J. Trends in the management and survival of digestive tract cancers among patients aged over 80 years. *Aliment Pharmacol Ther* 2005; **22**: 233-241 [PMID: 16091061 DOI: 10.1111/j.1365-2036.2005.02559.x]
- 50 **Heald RJ**, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg* 1998; **133**: 894-899 [PMID: 9711965 DOI: 10.1001/archsurg.133.8.894]
- 51 **Kim HS**, Ko S, Oh NG. Long-term results of extended intersphincteric resection for very low rectal cancer: a retrospective study. *BMC Surg* 2016; **16**: 21 [PMID: 27090553 DOI: 10.1186/s12893-016-0133-6]
- 52 **Folkesson J**, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; **23**: 5644-5650 [PMID: 16110023 DOI: 10.1200/JCO.2005.08.144]
- 53 **Basili G**, Lorenzetti L, Biondi G, Preziuso E, Angrisano C, Carneccchi P, Roberto E, Goletti O. Colorectal cancer in the elderly. Is there a role for safe and curative surgery? *ANZ J Surg* 2008; **78**: 466-470 [PMID: 18522567 DOI: 10.1111/j.1445-2197.2008.04536.x]
- 54 **Schiffmann L**, Ozcan S, Schwarz F, Lange J, Prall F, Klar E. Colorectal cancer in the elderly: surgical treatment and long-term survival. *Int J Colorectal Dis* 2008; **23**: 601-610 [PMID: 18343931 DOI: 10.1007/s00384-008-0457-5]
- 55 **Devon KM**, Vergara-Fernandez O, Victor JC, McLeod RS. Colorectal cancer surgery in elderly patients: presentation, treatment, and outcomes. *Dis Colon Rectum* 2009; **52**: 1272-1277 [PMID: 19571704 DOI: 10.1007/DCR.0b013e3181a74d2e]
- 56 **Paksoy M**, Ipek T, Colak T, Cebeci H. Influence of age on prognosis and management of patients with colorectal carcinoma. *Eur J Surg* 1999; **165**: 55-59 [PMID: 10069635 DOI: 10.1080/110241599750007513]

P-Reviewer: Kleeff J, Uggeri F, van Oudheusden TR

S-Editor: Qi Y **L-Editor:** A **E-Editor:** Li D



Rubber band ligation of hemorrhoids: A guide for complications

Andreia Albuquerque

Andreia Albuquerque, Department of Gastroenterology, Centro Hospitalar São João, 4200-319 Porto, Portugal

Author contributions: Albuquerque A solely contributed to this manuscript.

Conflict-of-interest statement: There is no financial support or relationships that may pose conflict of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Andreia Albuquerque, MD, Department of Gastroenterology, Centro Hospitalar São João, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal. a.albuquerque.dias@gmail.com
Telephone: +351-225-512100
Fax: +351-225-025766

Received: April 13, 2016

Peer-review started: April 18, 2016

First decision: May 19, 2016

Revised: June 25, 2016

Accepted: July 14, 2016

Article in press: July 18, 2016

Published online: September 27, 2016

Abstract

Rubber band ligation is one of the most important, cost-effective and commonly used treatments for internal hemorrhoids. Different technical approaches were developed mainly to improve efficacy and safety. The technique can be employed using an endoscope with forward-

view or retroflexion or without an endoscope, using a suction elastic band ligator or a forceps ligator. Single or multiple ligations can be performed in a single session. Local anaesthetic after ligation can also be used to reduce the post-procedure pain. Mild bleeding, pain, vaso-vagal symptoms, slippage of bands, priapism, difficulty in urination, anal fissure, and chronic longitudinal ulcers are normally considered minor complications, more frequently encountered. Massive bleeding, thrombosed hemorrhoids, severe pain, urinary retention needing catheterization, pelvic sepsis and death are uncommon major complications. Mild pain after rubber band ligation is the most common complication with a high frequency in some studies. Secondary bleeding normally occurs 10 to 14 d after banding and patients taking anti-platelet and/or anti-coagulant medication have a higher risk, with some reports of massive life-threatening haemorrhage. Several infectious complications have also been reported including pelvic sepsis, Fournier's gangrene, liver abscesses, tetanus and bacterial endocarditis. To date, seven deaths due to these infectious complications were described. Early recognition and immediate treatment of complications are fundamental for a favourable prognosis.

Key words: Hemorrhoids; Rubber band ligation; Pain; Bleeding; Infection

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Rubber band ligation of hemorrhoids is a very effective non-surgical treatment for internal hemorrhoids. Different techniques were developed mainly to improve efficacy and safety. This is an overall safe procedure, although severe complications can occur, such as infections. It is very important to know these possible complications to reduce their risk and to allow early recognition and successful treatment.

Albuquerque A. Rubber band ligation of hemorrhoids: A guide for complications. *World J Gastrointest Surg* 2016; 8(9): 614-620

GENERAL CONCEPTS OF HEMORRHOIDAL LIGATION

In the 1950s, Blaisdell^[1] described a new technique for the ligation of bleeding internal hemorrhoids which can be performed in the office without the need for hospitalization. This new concept was based on the fact that internal hemorrhoids are easily accessible, practically devoid of pain and thus, suitable for outpatient treatment. In addition, during this period, injection therapy was an alternative to surgery, but without any controlled destruction of hemorrhoidal tissue. The technique of office ligation of internal hemorrhoids was later modified and simplified using rubber bands by Barron^[2] in the 1960s. Since then, rubber band ligation (RBL) was established as one of the most important, cost-effective and commonly used treatments for first- to third-degree internal hemorrhoids, causing fibrosis, retraction, and fixation of the hemorrhoidal cushions^[3].

When compared to other non-surgical methods, like sclerotherapy and infrared coagulation, RBL has better long-term efficacy, requiring fewer sessions for treatment, although with a higher rate of post-treatment pain^[4,5]. Hemorrhoidectomy showed better response rates, but it was associated with more complications, time off work and pain than RBL^[4,6]. RBL should be considered as a first-line therapy for first- to third-degree internal hemorrhoids^[4] commonly indicated for bleeding and/or prolapsing. Surgical therapy can be considered in the presence of an important external component, thrombosis or recurrence after repeated banding^[6].

There are studies that evaluated the use of combined non-surgical therapies^[7-9]. A prospective randomized trial^[7] comparing the simultaneous application of sclerotherapy and RBL (sclerotherapy of the smaller non-prolapsing hemorrhoidal piles and RBL of the larger prolapsing piles), with sclerotherapy and RBL applied separately, showed that there was no significant difference between the combination and RBL alone groups.

RBL technique can be employed using an endoscope with forward-view or retroflexion or without an endoscope, using a suction elastic band ligator or a forceps ligator. Several patient positions can be used, without the need for bowel preparation or sedation^[3] and the ligations should be performed in the area above the dentate line that is devoid of sensory nerves.

The success rate of RBL ranges from 69% to 97%^[10]. A larger number of recurrences have been described with longer follow-up periods, but recurrences can be treated with repeat sessions and time to recurrence shortened with subsequent treatment courses^[10]. Recurrence rates are variable, with 6.6% to 18% of patients submitted to RBL requiring additional treatment sessions due to the recurrent symptoms^[10].

COMPLICATIONS OF RBL

There are several complications associated with this technique, which can be classified as minor or major (severe)^[11]. Mild bleeding, pain, vaso-vagal symptoms, slippage of bands, priapism, difficulty in urination, anal fissure, and chronic longitudinal ulcers are more common and normally considered minor complications. Massive bleeding, thrombosed hemorrhoids, severe pain, urinary retention needing catheterization, pelvic sepsis, fistula and death are major complications that have been less commonly reported.

Several studies described different rates of complications following RBL, ranging from 3%^[12] to 18.8%^[13]. The most common complications are pain and bleeding.

A review of 39 studies including 8060 patients submitted to RBL revealed post-banding complications in 14% of the patients, in the form of severe pain in 5.8%, haemorrhage in 1.7%, infection in 0.05%, anal fissure and fistula in 0.4%^[14].

In a prospective study by Bat *et al*^[11], including 512 patients submitted to RBL, 37 (7.2%) patients had complications. In this study RBL was performed using the Barron applicator, with a single ligation per session, with a total of one to seven ligations per person at four-week intervals. Minor complications were reported in 4.7% (thrombosed prolapsed hemorrhoids, slippage of bands, minor rectal bleeding, chronic longitudinal ulcer, priapism, difficulty in urination, and tender induration) and severe complications, requiring admission were described in 2.5% of the patients (massive bleeding, severe thrombosis of hemorrhoids, severe pain, perianal abscess, and fistula). Severe complications were more common in right anterior hemorrhoid RBL and in patients with previous hemorrhoidectomy. Most complications occurred following the first session.

Studies do not show any significant manometric change after RBL^[15-17], namely, in the maximum resting pressure and squeeze pressure.

Bleeding

Bleeding after RBL normally occurs after 10-14 d, probably due to the sloughing of the ligated hemorrhoids^[11,18,19].

Patients taking anti-platelet and/or anti-coagulant medication have a higher risk of secondary bleeding. There are cases of massive life-threatening haemorrhage following hemorrhoidal RBL in patients on acetylsalicylic acid (ASA)^[18,20,21] and clopidogrel^[19].

In a study by Bat *et al*^[11], including 512 patients submitted to RBL, five of the six patients who had massive bleeding, developed symptoms 10 d or more after the procedure. Three patients that were transfused were taking ASA regularly.

In a retrospective study^[10] including 805 patients who had undergone RBL aiming to evaluate the efficacy and safety of this procedure, higher bleeding rates were encountered with the use of ASA /nonsteroidal anti-inflammatory drugs (NSAIDs) and warfarin. Two (25%) of eight patients taking warfarin bled, whereas three

(7.5%) of 40 patients taking ASA or other NSAIDs bled.

Marshman *et al*^[22] conducted a study, including 241 patients undergoing RBL over a five-year period and focused on complications. Three (1.2%) patients required hospitalization for complications, of these patients, two on oral anticoagulants were admitted for significant bleeding.

In a retrospective study^[23], including 364 patients submitted to RBL while on antithrombotic therapy, holding antithrombotic medication 7-10 d following the procedure, appeared to equalize the risk of bleeding to that of patients not taking antithrombotic medications. There were 23 bleeding complications, and patients on clopidogrel experienced 50% of the significant bleeding episodes and 18% of the insignificant bleeding episodes, having a higher risk for bleeding complications, but due to the small sample size, this difference did not reach statistical significance. These authors defend that not stopping the drug before the procedure reduces the risk of ischemic events and allows ligation in the first consultation. Also, the greatest risk for bleeding typically occurs from 5 to 10 d after ligation.

It is routinely recommended that patients should stop this medication for at least 1 wk prior to, and 2 wk post RBL^[18]. The risk of the hemorrhoidal bleeding against the risk of thrombotic events must be balanced.

Concerning liver cirrhosis few data are published. In a prospective study including 500 patients submitted to RBL of symptomatic internal hemorrhoids, this procedure proved to be safe in 16 patients with coagulation disorders due to liver cirrhosis^[13].

Pain

Pain is one of the most common complications of RBL. Some studies reported mild anal pain in at least 25%-50% of patients, for the first 48 h after banding^[24,25], sometimes associated with nausea, shaking, light headedness, and urinary retention^[25].

In a prospective study^[26] specifically evaluating pain and patient satisfaction following RBL of hemorrhoids, pain was the most common symptom occurring in almost 90% of patients, with the pain scores higher 4 h following the procedure. At 1 wk, 75% of patients reported themselves as being pain-free; however, 7% were still experiencing moderate-to-severe pain. A total of 65% required oral analgesia during the week following RBL, most frequently on the day of the procedure. Vaso-vagal symptoms (dizziness or fainting) occurred in 30%, more commonly at the time of the procedure and in the evening of that day. Patients requiring oral analgesia and those experiencing bleeding or vaso-vagal symptoms were significantly less likely to be satisfied with RBL.

To minimize complications, before application, the tissue should be tested and if the patient complains of discomfort following the ligation, the band should be removed immediately and reapplied^[27].

Infectious complications

Septic complications have been described after hemo-

rrhoid treatments, namely, after injection sclerotherapy, RBL, cryotherapy, hemorrhoidectomy and stapled hemorrhoidopexy^[28,29].

Several infectious complications have been reported following RBL including pelvic sepsis, Fournier's gangrene, liver abscesses, tetanus and bacterial endocarditis. Deaths due to these infectious complications were also reported.

One of hypotheses is related to the transmural necrosis or slough following banding that facilitates the development of deep infection by migration of the bowel bacterial flora, which can spread to adjacent tissues^[30-32]. Transient bacteraemias have been described following digital rectal examination, proctoscopy, colonoscopy, injection sclerotherapy and hemorrhoidectomy^[33-37].

One of the most serious complications is pelvic sepsis, with several reports in the literature^[14,30,31,38-41]. Suspicion should arise in patients with pain, fever, edema and urinary retention^[28-31], normally 3-10 d following banding. To our knowledge, only one case that developed septic complications was human immunodeficiency virus (HIV) positive^[40].

A case of Fournier's gangrene in an elderly patient with diabetes following RBL was described. The patient recovered after surgical debridement and antibiotherapy^[42].

Liver abscesses associated with the treatment of hemorrhoids were first described related to hemorrhoidectomy^[43,44] and sclerotherapy^[45]. To our knowledge, there are six case reports of liver abscesses due to RBL of hemorrhoids^[20,46-50]. Most cases were male (5/6 patients), more frequently due to *Klebsiella* (4/6 patients) and multiple abscesses (5/6 patients) were normally present. All patients recovered and only in one case a right hepatectomy was necessary (Table 1).

Tetanus due to RBL was described in two patients^[51,52], both of whom survived.

There is a only a case report of patient with a ventricular septal defect that developed endocarditis leading to septic pulmonary and renal emboli following single-quadrant banding of hemorrhoids^[53]. The patient recovered after cardiac surgery.

The literature shows that all seven deaths linked to RBL were due to septic complications^[32,38,54,55]. Most cases were male (six patients) and no predisposing factors have been established. Time until symptom onset was between 3 to 10 d after banding, and the most common initial symptoms were pain and urinary retention (Table 2).

Early recognition and immediate treatment of infectious complications are fundamental. There are several authors recommending enemas, application of povidone-iodine solution and oral antibiotics before the procedure to reduce the risk, but studies supporting these recommendations are lacking.

SPECIAL SITUATIONS

There are certain conditions that have been considered a contraindication for RBL of hemorrhoids due to a higher risk of complications, namely, HIV and Crohn's disease.

In 1989, there was a case report of a 45-year-old

Table 1 Case reports of liver abscesses due to rubber band ligation of hemorrhoids

Age (yr)	Sex	Bacteria	Comorbidities	No.	Treatment	Outcome	Ref.
58	Male	Klebsiella aerogenes	Diabetes	Multiple	Antibiotics, drainage	Resolution	[20]
58	Male	Klebsiella pneumoniae	Previous pulmonary tuberculosis	Multiple	Antibiotics, drainage, right hepatectomy	Resolution	[46]
40	Male	Citrobacter freundii		Single	Antibiotics, drainage	Resolution	[47]
64	Male	Fusobacterium necrophorum	Asthma	Multiple	Antibiotics, drainage	Resolution	[48]
49	Male	Klebsiella pneumoniae	Diabetes, hypertension, dyslipidaemia, stroke, previously treated pulmonary tuberculosis	Multiple	Antibiotics	Resolution	[49]
61	Female	Klebsiella pneumoniae	Peptic ulcer, dyslipidemia	Multiple	Antibiotics, drainage	Resolution	[50]

Table 2 Deaths related to rubber band ligation

Age (yr)	Sex	Comorbidities	Time until symptom onset (d)	Symptoms	Bacteria	Ref.
38	Male	None	4	Pain, urinary retention	None	[32]
54	Male	None	10	Vomiting, urinary retention, fever	None	[32]
34	Male	None		Pain, urinary retention, fever	<i>Enterobacteriaceae</i> (abdomen fluid) <i>Escherichia coli</i> (retroperitoneum and blood)	[32]
37	Male	None	5	Pain, urinary retention	<i>Escherichia coli</i> (urine and rectal cultures)	[32]
73	Male	Not described	3	Pain, fever, urinary retention,	None	[38]
27	Male	Schizophrenia	4	Fever, pain, difficulty passing urine	<i>Clostridia perfringens</i> , <i>Clostridia sporogenes</i> , <i>Bacteroids</i> (pelvic muscles), <i>Escherichia coli</i> (rectal cultures)	[54]
68	Female	None	7	Anal pain, difficulty passing urine, vomiting	<i>Enterococcus</i> (perianal fluid)	[55]

HIV positive male patient who developed a supralelevator abscess after RBL^[40]. The authors concluded that this procedure is potentially dangerous in HIV patients and it should be abandoned. Although this complication was also described in HIV negative patients following RBL^[38] and, to our knowledge, this is the only infectious complication described in an HIV positive patient. In a retrospective review^[56] of asymptomatic HIV positive patients that were submitted to RBL of symptomatic hemorrhoids, this technique proved to be safe and effective. It was performed in 11 HIV positive patients and no complications were reported. Median CD4 cell count was 450 (range, 200-1000) cells/ μ L and there was a median of two (range, 1-4) bands per patient.

In a retrospective study^[57], including 42 patients with ulcerative colitis and 20 with Crohn's disease, treated both surgically and conservatively for hemorrhoids over a 41 year period, patients with ulcerative colitis had a low complication rate (4 complications after 58 courses of treatment) and Crohn's disease had a high complication rate (11 complications after 26 courses of treatment). No reference was made to RBL treatment in this study. Thus, concerning Crohn's disease and RBL very few data are published. D'Ugo *et al*^[58] published a 9-year retrospective study of 45 Crohn's disease patients treated for hemorrhoids either medically or surgically. In this series RBL was considered a surgical treatment, and in total two patients submitted to it reported no complications.

patients with second- and third-degree hemorrhoids compared suction and forceps ligation concerning pain after the procedure, intra-procedure bleeding and other complications. The forceps group had higher pain scores immediately after ligation and at 24 h post-banding, needed higher amount of analgesia and had higher intra-procedure bleeding^[59]. Authors hypothesized that this is due to poorer visualization and forceps-induced physical trauma of the friable hemorrhoids.

Single vs multiple ligations

Initially, single ligation per session was recommended due to the belief that a higher complication rate is associated with multiple banding, namely, pain and tenesmus after the procedure^[2].

A retrospective study^[60] comparing patients with multiple banding in a single session ($n = 155$) and single banding ($n = 22$) showed that patients with multiple hemorrhoidal banding did experience more discomfort and pain (29% vs 4.5%), but that this was well tolerated and manageable with oral analgesia of limited duration. Vasovagal reactions, limited bleeding, urinary symptoms, and local swelling and oedema were also more common. There were no cases of massive bleeding or sepsis.

Randomized controlled trials comparing single and triple band ligation^[27,61] showed that triple RBL is an equally safe and effective procedure for managing internal hemorrhoid disease. Fewer treatment sessions are required for triple RBL, so this strategy is more cost-effective^[61]. Furthermore, there is a risk of possible bleeding from untreated hemorrhoids after an initial RBL for other hemorrhoids^[2].

DIFFERENT TECHNICAL APPROACHES

Suction vs forceps ligation

A prospective randomized clinical trial including 100

Endoscopic vs non-endoscopic ligation

The endoscopic hemorrhoidal ligation was initially described in 1998, in the forward-view^[62] and then in retroflexion^[63,64]. Some authors favoured the retroflexed position due to easy assessment and treatment^[63].

Endoscopic ligation proved to be an effective and safe technique for treating internal hemorrhoids. In a study by Berkelhammer *et al*^[63], retroflexed endoscopic band ligation of second- and third-degree bleeding internal hemorrhoids, with a mean of three bands (range 1-6) placed in a single session, showed an excellent result in 80% of patients with second-degree hemorrhoids (better than third-degree hemorrhoids with an excellent result in 54%). Major, nonfatal complications were detected in 4% (severe pain, delayed haemorrhage requiring transfusion, urinary retention, and severe thrombosis of external hemorrhoids) of patients. In a study by Fukuda *et al*^[64], retroflexed endoscopic multiple band ligation was performed on patients with symptomatic first- to fourth-degree internal hemorrhoids, with a mean of 8 bands (range 4-14) placed per treatment session. The long-term response was excellent for 89% of the patients, without any major complications in the 82 patients included (severe pain, late-onset haemorrhage requiring transfusion, or severe thrombosis of external hemorrhoids).

Endoscopic ligation has some advantages over rigid instruments that are more difficult to manoeuvre and have limited visualization, allowing for more band placement and photographic documentation of the procedure^[62,63]. There are randomized studies comparing ligation with flexible videoendoscopes (retrograde or antegrade) and the conventional technique with rigid proctoscopes^[65,66]. These trials showed that the long-term efficacy and safety were similar, but with videoendoscopes fewer treatment sessions were needed and a higher proportion of patients treated with a single session^[65].

Local anaesthetic vs no-local anaesthetic in hemorrhoidal ligation

The use of local anaesthesia after hemorrhoidal banding in order to reduce post-procedural pain was studied. In 2015, a meta-analysis^[24] including four randomized controlled trials (387 patients in total), comparing pain and other associated symptoms in patients who received a local injection after hemorrhoidal banding and patients who did not, showed that the post-procedure pain score was significantly lower in the group of patients with local anaesthetic injection. These studies included different anaesthetic treatment protocols. Hooker *et al*^[25] randomized patients to receive a local injection of 0.5 mL of 0.5% bupivacaine with 1:200000 epinephrine, an injection of normal saline, or no injection, immediately superior to each band. In patients receiving bupivacaine within 30 min post-banding, there was a significant reduction in pain, nausea and shaking, which may be useful in the immediate period. However, bupivacaine injection did not reduce pain at 6 h or more post-banding, and did not have other benefits. In a study by

Law *et al*^[67] patients received 1-2 mL of 2% lignocaine injected into the banded hemorrhoidal segment, but no post-ligation pain reduction was reported. Kwok *et al*^[68] randomized patients to an anesthetic injection of 1 mL of 0.5% bupivacaine without adrenaline in the submucosa proximally to the rubber band site and showed that this reduced discomfort compared with no local anaesthetic by the time patients left the clinic (30 min after the procedure). Benefit beyond this period was not obtained. Authors hypothesized that local anaesthetic injection deep to the banded tissue, until a bleb large enough to encompass the "base" of the hemorrhoid was raised, would be more effective than injection into the devitalized banded tissue.

Bupivacaine effect lasts for 4 to 6 h^[25], so this could help in the short-term period following banding, but no study has thus far showed that this can be helpful beyond this period.

CONCLUSION

RBL of hemorrhoids is a very effective and safe procedure, with severe complications being uncommon. Before applying the bands, it is very important to know the patient's medical history, namely, comorbidities and medication. After RBL, patient education is mandatory, including analgesia, softening of the stools, warm sitz baths and information concerning early and late complications. If complications occur, early recognition and immediate treatment are fundamental for a successful outcome.

REFERENCES

1. Blaisdell PC. Office ligation of internal hemorrhoids. *Am J Surg* 1958; **96**: 401-404 [PMID: 13571517 DOI: 10.1016/0002-9610(58)90933-4]
2. Barron J. Office ligation of internal hemorrhoids. *Am J Surg* 1963; **105**: 563-570 [PMID: 13969563 DOI: 10.1016/0002-9610(63)90332-5]
3. Siddiqui UD, Barth BA, Banerjee S, Bhat YM, Chauhan SS, Gottlieb KT, Konda V, Maple JT, Murad FM, Pfau P, Pleskow D, Tokar JL, Wang A, Rodriguez SA. Devices for the endoscopic treatment of hemorrhoids. *Gastrointest Endosc* 2014; **79**: 8-14 [PMID: 24239254 DOI: 10.1016/j.gie.2013.07.021]
4. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities. A meta-analysis. *Dis Colon Rectum* 1995; **38**: 687-694 [PMID: 7607026 DOI: 10.1007/BF02048023]
5. Johanson JF, Rimm A. Optimal nonsurgical treatment of hemorrhoids: a comparative analysis of infrared coagulation, rubber band ligation, and injection sclerotherapy. *Am J Gastroenterol* 1992; **87**: 1600-1606 [PMID: 1442682]
6. Shanmugam V, Thaha MA, Rabindranath KS, Campbell KL, Steele RJ, Loudon MA. Rubber band ligation versus excisional haemorrhoidectomy for haemorrhoids. *Cochrane Database Syst Rev* 2005; (3): CD005034 [PMID: 16034963 DOI: 10.1002/14651858.cd005034.pub2]
7. Kanellos I, Goulmaris I, Christoforidis E, Kelpis T, Betsis D. A comparison of the simultaneous application of sclerotherapy and rubber band ligation, with sclerotherapy and rubber band ligation applied separately, for the treatment of haemorrhoids: a prospective randomized trial. *Colorectal Dis* 2003; **5**: 133-138 [PMID: 12780901 DOI: 10.1046/j.1463-1318.2003.00395.x]
8. Accarpio G, Ballari F, Puglisi R, Menoni S, Ravera G, Accarpio

- FT, Cariati A, Zaffarano R. Outpatient treatment of hemorrhoids with a combined technique: results in 7850 cases. *Tech Coloproctol* 2002; **6**: 195-196 [PMID: 12525916 DOI: 10.1007/s101510200043]
- 9 **Chew SS**, Marshall L, Kalish L, Tham J, Grieve DA, Douglas PR, Newstead GL. Short-term and long-term results of combined sclerotherapy and rubber band ligation of hemorrhoids and mucosal prolapse. *Dis Colon Rectum* 2003; **46**: 1232-1237 [PMID: 12972968 DOI: 10.1007/s10350-004-6720-0]
- 10 **Iyer VS**, Shrier I, Gordon PH. Long-term outcome of rubber band ligation for symptomatic primary and recurrent internal hemorrhoids. *Dis Colon Rectum* 2004; **47**: 1364-1370 [PMID: 15484351 DOI: 10.1007/s10350-004-0591-2]
- 11 **Bat L**, Melzer E, Koler M, Dreznick Z, Shemesh E. Complications of rubber band ligation of symptomatic internal hemorrhoids. *Dis Colon Rectum* 1993; **36**: 287-290 [PMID: 8449135 DOI: 10.1007/BF02053512]
- 12 **Longman RJ**, Thomson WH. A prospective study of outcome from rubber band ligation of piles. *Colorectal Dis* 2006; **8**: 145-148 [PMID: 16412076 DOI: 10.1111/j.1463-1318.2005.00873.x]
- 13 **Kombarozos VA**, Skrekas GJ, Pissiotis CA. Rubber band ligation of symptomatic internal hemorrhoids: results of 500 cases. *Dig Surg* 2000; **17**: 71-76 [PMID: 10720835 DOI: 10.1159/000018803]
- 14 **Wechter DG**, Luna GK. An unusual complication of rubber band ligation of hemorrhoids. *Dis Colon Rectum* 1987; **30**: 137-140 [PMID: 3803121 DOI: 10.1007/BF02554954]
- 15 **El Nakeeb AM**, Fikry AA, Omar WH, Fouda EM, El Metwally TA, Ghazy HE, Badr SA, Abu Elkhar MY, Elawady SM, Abd Elmoniam HH, Khafagy WW, Morshed MM, El Lithy RE, Farid ME. Rubber band ligation for 750 cases of symptomatic hemorrhoids out of 2200 cases. *World J Gastroenterol* 2008; **14**: 6525-6530 [PMID: 19030206 DOI: 10.3748/wjg.14.6525]
- 16 **Bursics A**, Weltner J, Flaotner LE, Morvay K. Ano-rectal physiological changes after rubber band ligation and closed haemorrhoidectomy. *Colorectal Dis* 2004; **6**: 58-61 [PMID: 14692955 DOI: 10.1111/j.1463-1318.2004.00583.x]
- 17 **Izadpanah A**, Hosseini S, Mahjoob M. Comparison of electrotherapy, rubber band ligation and hemorrhoidectomy in the treatment of hemorrhoids: a clinical and manometric study. *Middle East J Dig Dis* 2010; **2**: 9-13 [PMID: 25197506]
- 18 **Odelowo OO**, Mekasha G, Johnson MA. Massive life-threatening lower gastrointestinal hemorrhage following hemorrhoidal rubber band ligation. *J Natl Med Assoc* 2002; **94**: 1089-1092 [PMID: 12510709]
- 19 **Beattie GC**, Rao MM, Campbell WJ. Secondary haemorrhage after rubber band ligation of haemorrhoids in patients taking clopidogrel--a cautionary note. *Ulster Med J* 2004; **73**: 139-141 [PMID: 15651778]
- 20 **Parker R**, Gul R, Bucknall V, Bowley D, Karandikar S. Double jeopardy: pyogenic liver abscess and massive secondary rectal haemorrhage after rubber band ligation of haemorrhoids. *Colorectal Dis* 2011; **13**: e184 [PMID: 20718833 DOI: 10.1111/j.1463-1318.2010.02387.x]
- 21 **Patel S**, Shahzad G, Rizvon K, Subramani K, Viswanathan P, Mustacchia P. Rectal ulcers and massive bleeding after hemorrhoidal band ligation while on aspirin. *World J Clin Cases* 2014; **2**: 86-89 [PMID: 24749117 DOI: 10.12998/wjcc.v2.i4.86]
- 22 **Marshman D**, Huber PJ, Timmerman W, Simonton CT, Odom FC, Kaplan ER. Hemorrhoidal ligation. A review of efficacy. *Dis Colon Rectum* 1989; **32**: 369-371 [PMID: 2714125 DOI: 10.1007/BF02563683]
- 23 **Nelson RS**, Ewing BM, Ternent C, Shashidharan M, Blatchford GJ, Thorson AG. Risk of late bleeding following hemorrhoidal banding in patients on antithrombotic prophylaxis. *Am J Surg* 2008; **196**: 994-999; discussion 999 [PMID: 19095121 DOI: 10.1016/j.amjsurg.2008.07.036]
- 24 **Sajid MS**, Bhatti MI, Caswell J, Sains P, Baig MK. Local anaesthetic infiltration for the rubber band ligation of early symptomatic haemorrhoids: a systematic review and meta-analysis. *Updates Surg* 2015; **67**: 3-9 [PMID: 25724281 DOI: 10.1007/s13304-015-0286-3]
- 25 **Hooker GD**, Plewes EA, Rajgopal C, Taylor BM. Local injection of bupivacaine after rubber band ligation of hemorrhoids: prospective, randomized study. *Dis Colon Rectum* 1999; **42**: 174-179 [PMID: 10211492 DOI: 10.1007/BF02237123]
- 26 **Watson NF**, Liptrott S, Maxwell-Armstrong CA. A prospective audit of early pain and patient satisfaction following out-patient band ligation of haemorrhoids. *Ann R Coll Surg Engl* 2006; **88**: 275-279 [PMID: 16719998 DOI: 10.1308/003588406X98649]
- 27 **Khubchandani IT**. A randomized comparison of single and multiple rubber band ligations. *Dis Colon Rectum* 1983; **26**: 705-708 [PMID: 6354644 DOI: 10.1007/BF02554977]
- 28 **Guy RJ**, Seow-Choen F. Septic complications after treatment of haemorrhoids. *Br J Surg* 2003; **90**: 147-156 [PMID: 12555289 DOI: 10.1002/bjs.4008]
- 29 **McCloud JM**, Jameson JS, Scott AN. Life-threatening sepsis following treatment for haemorrhoids: a systematic review. *Colorectal Dis* 2006; **8**: 748-755 [PMID: 17032319 DOI: 10.1111/j.1463-1318.2006.01028.x]
- 30 **Clay LD**, White JJ, Davidson JT, Chandler JJ. Early recognition and successful management of pelvic cellulitis following hemorrhoidal banding. *Dis Colon Rectum* 1986; **29**: 579-581 [PMID: 3743298 DOI: 10.1007/BF02554261]
- 31 **Shemesh EI**, Kodner IJ, Fry RD, Neufeld DM. Severe complication of rubber band ligation of internal hemorrhoids. *Dis Colon Rectum* 1987; **30**: 199-200 [PMID: 3829863 DOI: 10.1007/BF02554339]
- 32 **Russell TR**, Donohue JH. Hemorrhoidal banding. A warning. *Dis Colon Rectum* 1985; **28**: 291-293 [PMID: 3888558 DOI: 10.1007/BF02560424]
- 33 **LeFrock JL**, Ellis CA, Turchik JB, Weinstein L. Transient bacteremia associated with sigmoidoscopy. *N Engl J Med* 1973; **289**: 467-469 [PMID: 4587236 DOI: 10.1056/NEJM197308302890908]
- 34 **Dickman MD**, Farrell R, Higgs RH, Wright LE, Humphries TJ, Wojcik JD, Chappelka R. Colonoscopy associated bacteremia. *Surg Gynecol Obstet* 1976; **142**: 173-176 [PMID: 1108244]
- 35 **Hoffman BI**, Kobasa W, Kaye D. Bacteremia after rectal examination. *Ann Intern Med* 1978; **88**: 658-659 [PMID: 646257 DOI: 10.7326/0003-4819-88-5-658]
- 36 **Bonardi RA**, Rosin JD, Stonesifer GL, Bauer FW. Bacteremias associated with routine hemorrhoidectomies. *Dis Colon Rectum* 1976; **19**: 233-236 [PMID: 817876 DOI: 10.1007/BF02590908]
- 37 **Adami B**, Eckardt VF, Suermann RB, Karbach U, Ewe K. Bacteremia after proctoscopy and hemorrhoidal injection sclerotherapy. *Dis Colon Rectum* 1981; **24**: 373-374 [PMID: 7261821 DOI: 10.1007/BF02603422]
- 38 **Quevedo-Bonilla G**, Farkas AM, Abcarian H, Hambrick E, Orsay CP. Septic complications of hemorrhoidal banding. *Arch Surg* 1988; **123**: 650-651 [PMID: 3358691 DOI: 10.1001/archsurg.1988.01400290136024]
- 39 **Scarpa FJ**, Hillis W, Sabetta JR. Pelvic cellulitis: a life-threatening complication of hemorrhoidal banding. *Surgery* 1988; **103**: 383-385 [PMID: 3278407]
- 40 **Buchmann P**, Seefeld U. Rubber band ligation for piles can be disastrous in HIV-positive patients. *Int J Colorectal Dis* 1989; **4**: 57-58 [PMID: 2708884 DOI: 10.1007/BF01648552]
- 41 **Duchateau A**, Huyghe M. Perirectal sepsis after rubber band ligation of haemorrhoids: a case report. *Acta Chir Belg* 2014; **114**: 344-348 [PMID: 26021540]
- 42 **Subramaniam D**, Hureibi K, Zia K, Uheba M. The development of Fournier's gangrene following rubber band ligation of haemorrhoids. *BMJ Case Rep* 2013; **2013**: [PMID: 24287481 DOI: 10.1136/bcr-2013-201474]
- 43 **Parikh SR**, Molinelli B, Dailey TH. Liver abscess after hemorrhoidectomy. Report of two cases. *Dis Colon Rectum* 1994; **37**: 185-189 [PMID: 8306843 DOI: 10.1007/BF02047546]
- 44 **Mohammedi I**, Duperret S, Faysse E, Vedrinne JM, Motin J. [Liver abscess caused by Streptococcus intermedius, following hemorrhoidectomy]. *Ann Fr Anesth Reanim* 1996; **15**: 1090-1091 [PMID: 9206932 DOI: 10.1016/S0750-7658(96)89480-9]
- 45 **Murray-Lyon IM**, Kirkham JS. Hepatic abscesses complicating

- injection sclerotherapy of haemorrhoids. *Eur J Gastroenterol Hepatol* 2001; **13**: 971-972 [PMID: 11507365 DOI: 10.1097/00042737-200108000-00017]
- 46 **Ku JJ**, Marfan M, Wall D. Pyogenic liver abscess after haemorrhoidal banding. *ANZ J Surg* 2005; **75**: 828-830 [PMID: 16196119 DOI: 10.1111/j.1445-2197.2005.03322.x]
- 47 **Wiese L**, Nielsen X, Andresen K, Kjaer A, David K. 16S rDNA sequencing revealed *Citrobacter freundii* as the cause of liver abscess after banding of rectal haemorrhoids. *J Infect* 2005; **50**: 163-164 [PMID: 15667920 DOI: 10.1016/j.jinf.2004.08.027]
- 48 **Ergas D**, Abdul-Hai A, Sthoeger Z, Menahem BH, Miller R. Multiple pyogenic liver abscesses following hemorrhoid banding. *Isr Med Assoc J* 2007; **9**: 753-754 [PMID: 17987768]
- 49 **Chau NG**, Bhatia S, Raman M. Pylephlebitis and pyogenic liver abscesses: a complication of hemorrhoidal banding. *Can J Gastroenterol* 2007; **21**: 601-603 [PMID: 17853956 DOI: 10.1155/2007/106946]
- 50 **Xu M**, Russell M, Lin A, Yoo J. Pyogenic liver abscess as a complication of internal hemorrhoid banding. *Am Surg* 2014; **80**: E36-E37 [PMID: 24480193]
- 51 **Murphy KJ**. Tetanus after rubber-band ligation of haemorrhoids. *Br Med J* 1978; **1**: 1590-1591 [PMID: 656823 DOI: 10.1136/bmj.1.6127.1590-a]
- 52 **Kasher JA**, Mathisen G. Acquiring tetanus after hemorrhoid banding and other gastrointestinal procedures. *J Gastrointest Surg* 2007; **11**: 515-519 [PMID: 17436138 DOI: 10.1007/s11605-006-0079-6]
- 53 **Tejirian T**, Abbas MA. Bacterial endocarditis following rubber band ligation in a patient with a ventricular septal defect: report of a case and guideline analysis. *Dis Colon Rectum* 2006; **49**: 1931-1933 [PMID: 17080276 DOI: 10.1007/s10350-006-0769-x]
- 54 **O'Hara VS**. Fatal clostridial infection following hemorrhoidal banding. *Dis Colon Rectum* 1980; **23**: 570-571 [PMID: 7460695 DOI: 10.1007/BF02988999]
- 55 **Sim HL**, Tan KY, Poon PL, Cheng A, Mak K. Life-threatening perineal sepsis after rubber band ligation of haemorrhoids. *Tech Coloproctol* 2009; **13**: 161-164 [PMID: 18679564 DOI: 10.1007/s10151-008-0435-5]
- 56 **Moore BA**, Fleshner PR. Rubber band ligation for hemorrhoidal disease can be safely performed in select HIV-positive patients. *Dis Colon Rectum* 2001; **44**: 1079-1082 [PMID: 11535843 DOI: 10.1007/BF02234625]
- 57 **Jeffery PJ**, Parks AG, Ritchie JK. Treatment of haemorrhoids in patients with inflammatory bowel disease. *Lancet* 1977; **1**: 1084-1085 [PMID: 68184 DOI: 10.1016/S0140-6736(77)92337-6]
- 58 **D'Ugo S**, Franceschilli L, Cadeddu F, Leccesi L, Blanco Gdel V, Calabrese E, Milito G, Di Lorenzo N, Gaspari AL, Sileri P. Medical and surgical treatment of haemorrhoids and anal fissure in Crohn's disease: a critical appraisal. *BMC Gastroenterol* 2013; **13**: 47 [PMID: 23496835 DOI: 10.1186/1471-230X-13-47]
- 59 **Ramzisham AR**, Sagap I, Nadeson S, Ali IM, Hasni MJ. Prospective randomized clinical trial on suction elastic band ligator versus forceps ligator in the treatment of haemorrhoids. *Asian J Surg* 2005; **28**: 241-245 [PMID: 16234072 DOI: 10.1016/S1015-9584(09)60353-5]
- 60 **Lee HH**, Spencer RJ, Beart RW. Multiple hemorrhoidal bandings in a single session. *Dis Colon Rectum* 1994; **37**: 37-41 [PMID: 8287745 DOI: 10.1007/BF02047212]
- 61 **Poon GP**, Chu KW, Lau WY, Lee JM, Yeung C, Fan ST, Yiu TF, Wong SH, Wong KK. Conventional vs. triple rubber band ligation for hemorrhoids. A prospective, randomized trial. *Dis Colon Rectum* 1986; **29**: 836-838 [PMID: 3539557 DOI: 10.1007/BF02555358]
- 62 **Trowers EA**, Ganga U, Rizk R, Ojo E, Hodges D. Endoscopic hemorrhoidal ligation: preliminary clinical experience. *Gastrointest Endosc* 1998; **48**: 49-52 [PMID: 9684664 DOI: 10.1016/S0016-5107(98)70128-2]
- 63 **Berkelhammer C**, Moosvi SB. Retroflexed endoscopic band ligation of bleeding internal hemorrhoids. *Gastrointest Endosc* 2002; **55**: 532-537 [PMID: 11923767 DOI: 10.1067/mge.2002.122618]
- 64 **Fukuda A**, Kajiyama T, Arakawa H, Kishimoto H, Someda H, Sakai M, Tsunekawa S, Chiba T. Retroflexed endoscopic multiple band ligation of symptomatic internal hemorrhoids. *Gastrointest Endosc* 2004; **59**: 380-384 [PMID: 14997135 DOI: 10.1016/S0016-5107(03)02818-9]
- 65 **Wehrmann T**, Riphaus A, Feinstein J, Stergiou N. Hemorrhoidal elastic band ligation with flexible videoendoscopes: a prospective, randomized comparison with the conventional technique that uses rigid proctoscopes. *Gastrointest Endosc* 2004; **60**: 191-195 [PMID: 15278043 DOI: 10.1016/S0016-5107(04)01551-2]
- 66 **Cazemier M**, Felt-Bersma RJ, Cuesta MA, Mulder CJ. Elastic band ligation of hemorrhoids: flexible gastroscope or rigid proctoscope? *World J Gastroenterol* 2007; **13**: 585-587 [PMID: 17278225 DOI: 10.3748/wjg.v13.i4.585]
- 67 **Law WL**, Chu KW. Triple rubber band ligation for hemorrhoids: prospective, randomized trial of use of local anesthetic injection. *Dis Colon Rectum* 1999; **42**: 363-366 [PMID: 10223757 DOI: 10.1007/BF02236354]
- 68 **Kwok HC**, Noblett SE, Murray NE, Merrie AE, Hayes JL, Bissett IP. The use of local anaesthesia in haemorrhoidal banding: a randomized controlled trial. *Colorectal Dis* 2013; **15**: 487-491 [PMID: 23323626 DOI: 10.1111/codi.12088]

P- Reviewer: Brisinda G, El Nakeeb A, Pavlidis TE
S- Editor: Qiu S **L- Editor:** Wang TQ **E- Editor:** Li D



Minimally invasive management of anastomotic leaks in colorectal surgery

Yusuf Sevim, Suleyman Utku Celik, Hana Yavarifar, Cihangir Akyol

Yusuf Sevim, Department of General Surgery, Ankara Numune Training and Research Hospital, 06100 Ankara, Turkey

Suleyman Utku Celik, Hana Yavarifar, Cihangir Akyol, Department of General Surgery, Ankara University School of Medicine, 06100 Ankara, Turkey

Author contributions: Sevim Y and Akyol C contributed equally to this work, generated the figures and wrote the manuscript; Celik SU and Yavarifar H contributed to the writing of the manuscript; Akyol C conceived the minireview.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Cihangir Akyol, MD, Associate Professor, Department of General Surgery, Ankara University School of Medicine, Sıhhiye, 06100 Ankara, Turkey. cihangirakyol@gmail.com
Telephone: +90-312-5082288

Received: April 29, 2016
Peer-review started: May 4, 2016
First decision: July 4, 2016
Revised: July 6, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: September 27, 2016

Abstract

Anastomotic leakage is an unfortunate complication of colo-

rectal surgery. This distressing situation can cause severe morbidity and significantly affects the patient's quality of life. Additional interventions may cause further morbidity and mortality. Parenteral nutrition and temporary diverting ostomy are the standard treatments of anastomotic leaks. However, technological developments in minimally invasive treatment modalities for anastomotic dehiscence have caused them to be used widely. These modalities include laparoscopic repair, endoscopic self-expandable metallic stents, endoscopic clips, over the scope clips, endoanal repair and endoanal sponges. The review aimed to provide an overview of the current knowledge on the minimally invasive management of anastomotic leaks.

Key words: Minimally invasive surgery; Anastomotic leak; Colorectal surgery

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Anastomotic leakage is the most feared complication of colorectal surgery, leading to significant patient morbidity and mortality. Its incidence is 3%-6%, even in experienced hands. Despite the high prevalence of this condition, there is no consensus on the proper management of anastomotic leaks. In this review, we summarize and discuss the current knowledge on minimally invasive treatment strategies for anastomotic leakage after colorectal surgery.

Sevim Y, Celik SU, Yavarifar H, Akyol C. Minimally invasive management of anastomotic leaks in colorectal surgery. *World J Gastrointest Surg* 2016; 8(9): 621-626 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/621.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.621>

INTRODUCTION

Anastomotic leak (AL) following colorectal surgery is a feared complication with an incidence of 3%-6%, even

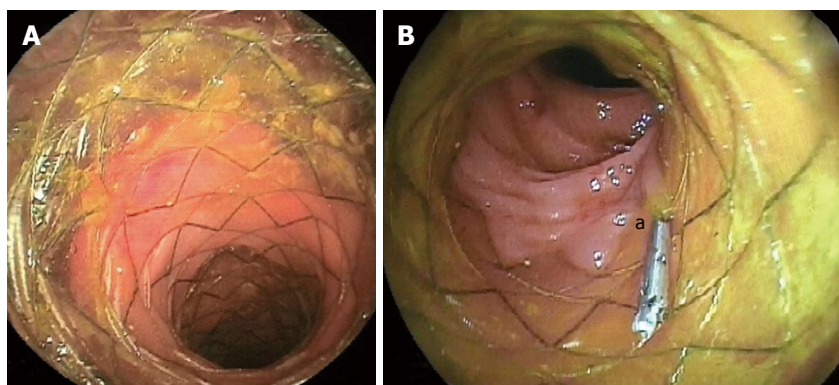


Figure 1 Self-expanding metal stent for anastomosis leakage. A: Endoscopic image after deployment of the stent; B: Stent with clip (a) at the proximal end.

in experienced hands^[1]. ALs can cause severe morbidity, cost, and affect the patient's quality of life. Moreover, major additional interventions may lead to further morbidity and mortality (with of 10%-20%)^[2]. Currently, technological developments in minimally invasive treatment modalities for ALs have caused them to be used widely. These modalities include laparoscopic repair, endoscopic self-expandable metallic stents (SEMS), endoscopic clips, over the scope clips (OTSCs), endoanal repair and endoanal sponges.

In this review, we summarize and discuss the current knowledge on minimally invasive treatment strategies for ALs after colorectal surgery.

LAPAROSCOPIC REPAIR AND MANAGEMENT

In the last two decades, there have been significant developments in the field of minimally invasive surgical procedures, including laparoscopy. Despite these advances in laparoscopic instrumentation and techniques, the laparoscopic management of AL after colorectal surgery is still under debate.

A retrospective study by Cuccurullo *et al*^[3] reported that AL was the most common finding (57.1%) at laparoscopic re-intervention. In this study, 91.7% of cases were managed by anastomotic repair, peritoneal lavage and temporary diverting ostomy. Only 8.3% of ALs required a Hartmann's procedure because of gross fecal contamination. The conversion rate to open surgery was 5.6%, because of extensive colonic ischemia and generalized peritonitis. Lee *et al*^[4] also reported an 8.2% conversion rate, and all ALs were treated with ileostomy/colostomy, with or without anastomotic repair. They compared the results of open and laparoscopic management, and observed significantly shorter hospital stay, lower 30-d postoperative morbidity and complication, and improved stoma closure rate in the laparoscopic group. In other studies by Wind *et al*^[5] and Vennix *et al*^[6], the morbidity rate, hospital stay, intensive care unit admission, and incisional hernia rate were reduced in the laparoscopic re-intervention group. Furthermore, re-laparoscopy can be used as a diagnostic tool if clinical

concerns exist, despite an adjunctive diagnostic imaging with reported diagnostic accuracy between 93% and 100%^[7].

Laparoscopic re-intervention is a safe, feasible and effective technique, and can also be considered as a diagnostic option as the first therapeutic approach for evaluating suspected postoperative complications. Today, many studies encourage the use of laparoscopy for the treatment of complications following minimally invasive colorectal surgery in skilled hands.

ENDOSCOPIC SEMS, AND OTHER STENTS

The use of colonic stents has significantly evolved over the last decades as an alternative method of converting emergency surgery for obstructing colorectal cancers to safer definitive elective surgery or as palliative treatment for inoperable malignant colorectal strictures, with high success rates^[8]. Moreover, the application of colonic stents has gained increasing attention in recent years for postoperative complications following colorectal surgery, including ALs, fistulas and perforations (Figure 1). In particular, smaller ALs that are not associated with severe sepsis might benefit from colonic stenting after laparoscopic peritoneal lavage and drainage, and fashioning of stoma^[9]. By contrast, some authors considered that endoscopic stenting could be utilized in patients with or without a stoma, in combination with percutaneous drainage of infected intraabdominal collections^[10].

Several types of intestinal stent are available, such as a SEMS (uncovered, partially or fully covered), a self-expanding plastic stent, and a biodegradable stent. Colonic stent-related complications include stent migration, anorectal pain, incontinence, perforation, rectal bleeding and stent obstruction^[9,11]. The stent can only be placed across an end-to-end anastomosis, and the distal end of the stent must be no less than 5 cm proximal to the anal verge^[10-12]. Stents placed very distally in the rectum may cause increased rectal pain, tenesmus or fecal incontinence^[11-13].

The risk of stent migration is high in the lower gastrointestinal tract because of the increased intestinal motility, and has been reported in 25% to 40% of

patients^[14-16]. This rate is lower in uncovered or partially covered stents than in biodegradable and fully covered stents^[9,10,12]. Migration has been also described when large-diameter stents have been used^[11,14]. However, the use of a partially covered SEMS prevents migration and allows for tissue in-growth; however, its removal is technically difficult^[11,12]. Clips or endoscopic suturing are alternative methods to anchor the stent in place and to reduce migration risk^[14] (Figure 1B). Optimal timing of stent removal is controversial. If possible, stents should be removed after adequate healing of the dehiscence is confirmed endoscopically and following resolution of clinical signs and symptoms^[16].

A recent study found that SEMS application was successful in 86% of 22 patients with ALs following colorectal surgery^[13]. In that study, fully covered SEMS were used in 19 patients and uncovered SEMS in three patients. Stent migration occurred in only one of the 22 patients (4.5%); this patient was in the covered stent group and stent migrated 6 mo after placement. Most of the patients complained of incontinence after placement of the stent, which regressed spontaneously after an average of 14 wk.

Recent advances and innovations in stent technology have led to the development expandable polydioxanone biodegradable stents as an effective alternative treatment of AL following colorectal surgery. The biodegradable stent does not to be removed, which can decrease mucosal hyperplastic reactions and adverse events associated with stent removal, compared with metal stents^[9,10,12,14].

Based on limited data, stent placement appears to be an alternative therapeutic option for selected patients with AL after colorectal surgery when performed by skilled endoscopists. Migration and cost are the major limitations of these stents.

ENDOSCOPIC CLIPS

Application of clips to approximate the edges of the leaking anastomosis is one of the endoscopic management techniques. Standard endoclips, which are used to control small perforations and bleeding, may be used to close an AL; however, the low closure of force of these clips limit their use for more scarred, fibrotic and irradiated tissues.

The first clip was manufactured by the Olympus Corporation (Japan) in 1995. Thereafter, a disposable pre-loaded version of this clip, known as Quickclips® (Olympus Ltd., Tokyo, Japan), has gained popularity. Thereafter, OTSC (Ovesco Endoscopy, endoscopy, Tübingen, Germany) were introduced; and in 2011, Cook Medical from United States produced the Instinct™ Endoscopic Hemoclip.

The OTSC is the most preferred clips to control AL. This clip is made of super-elastic nitinol, which is a biocompatible and magnetic resonance imaging-safe material, and has the benefit of a larger clip area with increased compression. Firstly, Kirschniak *et al*^[17] published their successful results using OTSC in 11 patients with bleeding or iatrogenic perforations. Application of OTSCs for leaks has since become popular. Weiland *et al*^[18] reported a general success rate of 84.6%. Arezzo *et al*^[19] used OTSCs

for colorectal surgery on 14 patients with leaks no larger than 15 mm (maximum diameter), and without luminal stenosis and abscess. Their success rate was also 86%. Occasionally, the first attempt fails, but repeated attempts will be successful in order to close the dehiscence of AL^[20].

Favorable results with OTSCs are obtained in the absence of fibrotic tissue. Closure of chronic leaks and fistulas seems to be a considerable challenge and may decrease the success rate^[21]. Contrastingly, OTSCs have significant cost benefits compared with ileostomy, and achieve full-thickness wall closure. Moreover, they require a shorter hospital stay and avoid temporary ileostomy^[19]. OTSCs can close defects up to 30 mm^[22]. Application of multiple clips may be possible for larger defects; however, there is limited experience of it^[23,24].

ENDOSCOPIC VACUUM-ASSISTED CLOSURE

Negative pressure wound therapy or vacuum-assisted closure is now a well-established treatment modality for chronic and difficult to heal wounds. Recently, this minimally invasive method has been proposed as an effective approach to manage ALs after colorectal surgery, with success rates ranging from 56.6% to 100%^[25-29]. In the original technique, after the presence of the abscess cavity is confirmed by diagnostic colonoscopy, the enteric and purulent contents are aspirated and then irrigated. Finally, an open pored, polyurethane sponge with an attached evacuation tube connected to a drainage system is inserted *via* an introducer sleeve that is fitted over an endoscope and placed through the dehiscence and into the pelvic cavity^[10,12,16,25].

The endo-sponge continuously removes secretions, improves microcirculation, and therefore induces granulation formation in the defect. It also aids closure of the pelvic cavity by the application of negative pressure of 125 mmHg^[26] (Figure 2). One disadvantage of this method is the requirement to change the sponge every 2-4 d until the abscess cavity has regressed^[25,28,29]. However, this treatment is more effective at shrinking cavities, especially when used within 6 wk after the AL^[10,30]. It should be noted that generalized peritonitis is not an indication for endo-sponge therapy^[12,25,29]; and the overall complication rates are around 20%, mainly comprising anastomosis stenosis, recidivate abscess and fistula^[26].

In 2008, a large series of endoscopic vacuum-assisted closure therapy cases was reported by Weidenhagen *et al*^[25]. In that study, definitive closure of the cavity was achieved in 28 of the 29 patients (96.6%) over a mean treatment period of 34 d (range 4-79 d). In a recent review, Strangio *et al*^[26] found that complete healing of the cavity was achieved in near 95% of cases overall, following a median of 30 d of treatment and the performance of a median of 11 sessions. The authors emphasized that endo-sponge applications might be safely performed in patients with or without a diverting ileostomy. Weidenhagen *et al*^[25] reported that four patients were treated without the construction of a divert-

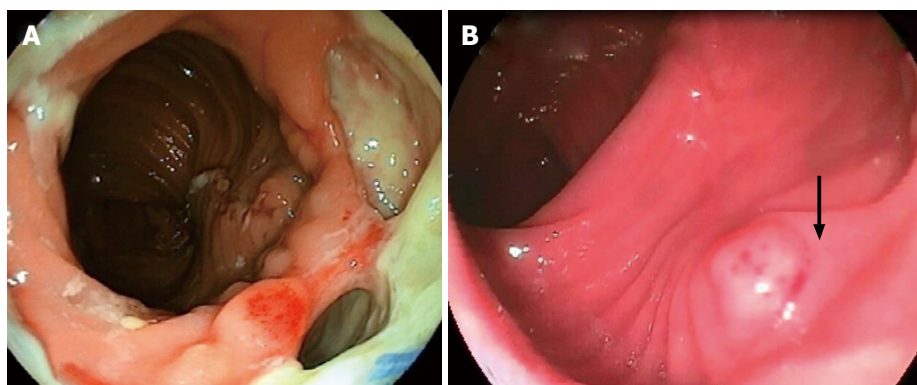


Figure 2 Endoscopic appearance of anastomotic leakage. A: Anastomotic leak with a cavity before endoscopic vacuum-assisted closure therapy; B: The same cavity covered with granulation tissue (black arrow) three weeks after vacuum therapy was initiated.

Table 1 Recent successful studies managed minimally invasively after acute or chronic anastomotic leak

Ref.	Year	Cases	Procedure	Gender (F/M)	Age (yr)	Previous diagnose or treatment	Success n (%)	Failure or complications n (%)	Follow-up
Lamazza <i>et al</i> ^[13]	2015	22	SEMS	11/11	68	Anterior resection (all) Neoadjuvant (21)	19 (86.4)	Failure: 3 (13.6) Stent migration: 1 (4.5)	18-42 mo
Arezzo <i>et al</i> ^[19]	2012	14	OTSC	8/6	68.5	Anterior resection (12) Colostomy closure (1) Right hemicolectomy (1)	12 (85.7)	1 patient needed further surgery	4 mo
Sulz <i>et al</i> ^[20]	2014	6	OTSC	1/5	66.5	Colorectal resection	5 (83.3)	Failure: 1 (Succeeded with 2 nd OTSC)	N/A
Weidenhagen <i>et al</i> ^[25]	2008	29	VAC	5/24	66.7	Rectal cancer (22) Rectosigmoidal cancer (3) Large rectal adenoma (2) Diverticulitis (1) Endometrial cancer infiltration (1)	28 (96.6)	1 (Hartmann's procedure)	VAC duration: 34.4 ± 19.4 d
Blumetti <i>et al</i> ^[31]	2011	5	Transanal repair	N/A	52	Coloanal anastomosis (4) Colorectal anastomosis (1)	4 (80)	Failure: 1 (20)	Time to repair: 8-15 mo

F/M: Female/male; SEMS: Self-expandable metallic stent; OTSC: Over the scope clip; N/A: Data not available; VAC: Vacuum-assisted closure.

ing stoma. Similarly, Glitsch *et al*^[28] reported successful endoscopic transanal vacuum-assisted rectal drainage for AL after rectal resection in 16 of 17 patients (94.1%). They also found that the closure time was directly dependent on the cavity size, distance from anastomosis to the anal verge and the patient's age. Patients with anastomoses that were 6 cm or less from the anal verge, who were elderly (aged over 62 years), and had a cavity measuring 5 cm × 6 cm or more had considerably longer healing times.

Endoscopic vacuum-assisted closure therapy seems a safe and useful therapeutic option for the local and minimally invasive management of AL after colorectal surgery, with high success rates. However, further prospective clinical studies with randomized data and larger numbers of patients are needed to clarify the beneficial effects of endo-sponge therapy in patients with anastomotic insufficiency.

TRANSANAL REPAIR

Transanal repair is another preferred method for treatment of delayed ALs. Candidates for this method should have a documented persistent sinus or cavity diagnosed

by contrast enema, without any evidence of recurrence and co-morbidity. Transanal repair uses a primary repair or repair with flap, especially for sinus formation of AL. The flap should be prepared with skin or mucosa, although there is limited supporting data concerning this in the literature. Endorectal flap advancement is well described in ileorectal anastomotic sinuses. Blumetti *et al*^[31] published their two-center study in 2012 and reported six transanal repairs for five patients with an 80% success rate.

In 2015, Brunner *et al*^[32] reported two consecutive patients managed by transanal primary repair and irrigation of the abdominal cavity for AL after single incision laparoscopic sigmoid resection for stage II/III diverticulitis. They mentioned no residual leaks, no anastomotic strictures and normal rectal functions.

A summary of some recent successful studies managed minimally invasively after anastomotic leakage and the outcomes in SEMS, OTSC, vacuum-assisted closure and transanal repair is shown in Table 1.

CONCLUSION

Anastomotic leaks continue to be critical and life-threat-

ening events, with considerable morbidity and mortality. Patients with ALs are often critically ill, and non-operative management strategies should be the preferred first-line approach. Currently, minimally invasive treatment options are a promising alternative to surgical treatment, with satisfactory outcomes for the management of ALs. Nevertheless, there is a need for further, large, high quality, randomized, controlled trials on the long-term outcome, function and clinical efficacy of these different techniques.

REFERENCES

- 1 **Kingham TP**, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. *J Am Coll Surg* 2009; **208**: 269-278 [PMID: 19228539 DOI: 10.1016/j.jamcollsurg.2008.10.015]
- 2 **Slieker JC**, Komen N, Mannaerts GH, Karsten TM, Willemsen P, Murawska M, Jeekel J, Lange JF. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. *Arch Surg* 2012; **147**: 447-452 [PMID: 22249852 DOI: 10.1001/archsurg.2011.1690]
- 3 **Cuccurullo D**, Pirozzi F, Sciuto A, Bracale U, La Barbera C, Galante F, Corcione F. Relaparoscopy for management of postoperative complications following colorectal surgery: ten years experience in a single center. *Surg Endosc* 2015; **29**: 1795-1803 [PMID: 25294542 DOI: 10.1007/s00464-014-3862-6]
- 4 **Lee CM**, Huh JW, Yun SH, Kim HC, Lee WY, Park YA, Cho YB, Chun HK. Laparoscopic versus open reintervention for anastomotic leakage following minimally invasive colorectal surgery. *Surg Endosc* 2015; **29**: 931-936 [PMID: 25060688 DOI: 10.1007/s00464-014-3755-8]
- 5 **Wind J**, Koopman AG, van Berge Henegouwen MI, Slors JF, Gouma DJ, Bemelman WA. Laparoscopic reintervention for anastomotic leakage after primary laparoscopic colorectal surgery. *Br J Surg* 2007; **94**: 1562-1566 [PMID: 17702090 DOI: 10.1002/bjs.5892]
- 6 **Vennix S**, Abegg R, Bakker OJ, van den Boezem PB, Brokelman WJ, Sietses C, Bosscha K, Lips DJ, Prins HA. Surgical re-interventions following colorectal surgery: open versus laparoscopic management of anastomotic leakage. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 739-744 [PMID: 23859744 DOI: 10.1089/lap.2012.0440]
- 7 **Kirshtein B**, Domchik S, Mizrahi S, Lantsberg L. Laparoscopic diagnosis and treatment of postoperative complications. *Am J Surg* 2009; **197**: 19-23 [PMID: 18558391 DOI: 10.1016/j.amjsurg.2007.10.019]
- 8 **van Hooft JE**, van Halsema EE, Vanbiervliet G, Beets-Tan RG, DeWitt JM, Donnellan F, Dumonceau JM, Glynne-Jones RG, Hassan C, Jiménez-Perez J, Meisner S, Muthusamy VR, Parker MC, Regimbeau JM, Sabbagh C, Sagar J, Tanis PJ, Vandervoort J, Webster GJ, Manes G, Barthet MA, Repici A. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2014; **46**: 990-1053 [PMID: 25325682 DOI: 10.1055/s-0034-1390700]
- 9 **Kabul Gürbulak E**, Akgün İE, Öz A, Ömeroğlu S, Battal M, Celayir F, Mihmanlı M. Minimal invasive management of anastomosis leakage after colon resection. *Case Rep Med* 2015; **2015**: 374072 [PMID: 25861277 DOI: 10.1155/2015/374072]
- 10 **Blumetti J**, Abcarian H. Management of low colorectal anastomotic leak: Preserving the anastomosis. *World J Gastrointest Surg* 2015; **7**: 378-383 [PMID: 26730283 DOI: 10.4240/wjgs.v7.i12.378]
- 11 **DiMaio CJ**, Dorfman MP, Gardner GJ, Nash GM, Schattner MA, Markowitz AJ, Chi DS, Gerdes H. Covered esophageal self-expandable metal stents in the nonoperative management of postoperative colorectal anastomotic leaks. *Gastrointest Endosc* 2012; **76**: 431-435 [PMID: 22817797 DOI: 10.1016/j.gie.2012.03.1393]
- 12 **Smallwood N**, Mutch MG, Fleshman JW. The failed anastomosis. In: Steele SR, Maykel JA, Champagne BJ, Orangio GR. Complexities in colorectal surgery: Decision-making and management. New York: Springer, 2014: 277-304 [DOI: 10.1007/978-1-4614-9022-7]
- 13 **Lamazza A**, Sterpetti AV, De Cesare A, Schillaci A, Antoniozzi A, Fiori E. Endoscopic placement of self-expanding stents in patients with symptomatic anastomotic leakage after colorectal resection for cancer: long-term results. *Endoscopy* 2015; **47**: 270-272 [PMID: 25668426 DOI: 10.1055/s-0034-1391403]
- 14 **Dabizzi E**, De Ceglie A, Kyanam Kabir Baig KR, Baron TH, Conio M, Wallace MB. Endoscopic "rescue" treatment for gastrointestinal perforations, anastomotic dehiscence and fistula. *Clin Res Hepatol Gastroenterol* 2016; **40**: 28-40 [PMID: 26209869 DOI: 10.1016/j.clinre.2015.04.006]
- 15 **Manta R**, Caruso A, Cellini C, Sica M, Zullo A, Mirante VG, Bertani H, Frazzoni M, Mutignani M, Galloro G, Conigliaro R. Endoscopic management of patients with post-surgical leaks involving the gastrointestinal tract: A large case series. *Unit Euro Gastroenterol J* 2016; 1-8 [DOI: 10.1177/2050640615626051]
- 16 **Rogalski P**, Daniluk J, Baniukiewicz A, Wroblewski E, Dabrowski A. Endoscopic management of gastrointestinal perforations, leaks and fistulas. *World J Gastroenterol* 2015; **21**: 10542-10552 [PMID: 26457014 DOI: 10.3748/wjg.v21.i37.10542]
- 17 **Kirschniak A**, Kratt T, Stüker D, Braun A, Schurr MO, Königsrainer A. A new endoscopic over-the-scope clip system for treatment of lesions and bleeding in the GI tract: first clinical experiences. *Gastrointest Endosc* 2007; **66**: 162-167 [PMID: 17591492 DOI: 10.1016/j.gie.2007.01.034]
- 18 **Weiland T**, Fehlker M, Gottwald T, Schurr MO. Performance of the OTSC System in the endoscopic closure of gastrointestinal fistulae--a meta-analysis. *Minim Invasive Ther Allied Technol* 2012; **21**: 249-258 [PMID: 22694247 DOI: 10.3109/13645706.2012.694367]
- 19 **Arezzo A**, Verra M, Reddavid R, Cravero F, Bonino MA, Morino M. Efficacy of the over-the-scope clip (OTSC) for treatment of colorectal postsurgical leaks and fistulas. *Surg Endosc* 2012; **26**: 3330-3333 [PMID: 22580885 DOI: 10.1007/s00464-012-2340-2]
- 20 **Sulz MC**, Bertolini R, Frei R, Semadeni GM, Borovicka J, Meyenberger C. Multipurpose use of the over-the-scope-clip system ("Bear claw") in the gastrointestinal tract: Swiss experience in a tertiary center. *World J Gastroenterol* 2014; **20**: 16287-16292 [PMID: 25473185 DOI: 10.3748/wjg.v20.i43.16287]
- 21 **Dişibeyaz S**, Köksal AŞ, Parlak E, Torun S, Şaşmaz N. Endoscopic closure of gastrointestinal defects with an over-the-scope clip device. A case series and review of the literature. *Clin Res Hepatol Gastroenterol* 2012; **36**: 614-621 [PMID: 22704818 DOI: 10.1016/j.clinre.2012.04.015]
- 22 **von Renteln D**, Schmidt A, Vassiliou MC, Rudolph HU, Caca K. Endoscopic full-thickness resection and defect closure in the colon. *Gastrointest Endosc* 2010; **71**: 1267-1273 [PMID: 20598252 DOI: 10.1016/j.gie.2009.12.056]
- 23 **Seebach L**, Bauerfeind P, Gubler C. "Sparing the surgeon": clinical experience with over-the-scope clips for gastrointestinal perforation. *Endoscopy* 2010; **42**: 1108-1111 [PMID: 21120779 DOI: 10.1055/s-0030-1255924]
- 24 **Manta R**, Manno M, Bertani H, Barbera C, Pigò F, Mirante V, Longinotti E, Bassotti G, Conigliaro R. Endoscopic treatment of gastrointestinal fistulas using an over-the-scope clip (OTSC) device: case series from a tertiary referral center. *Endoscopy* 2011; **43**: 545-548 [PMID: 21409741 DOI: 10.1055/s-0030-1256196]
- 25 **Weidenhagen R**, Gruetzner KU, Wiecken T, Spelsberg F, Jauch KW. Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method. *Surg Endosc* 2008; **22**: 1818-1825 [PMID: 18095024 DOI: 10.1007/s00464-007-9706-x]
- 26 **Strangio G**, Zullo A, Ferrara EC, Anderloni A, Carlino A, Jovani M, Ciscato C, Hassan C, Repici A. Endo-sponge therapy for management of anastomotic leakages after colorectal surgery: A case series and review of literature. *Dig Liver Dis* 2015; **47**: 465-469 [PMID: 25769505 DOI: 10.1016/j.dld.2015.02.007]
- 27 **Riss S**, Stift A, Kienbacher C, Dauser B, Haunold I, Kriwanek S, Radlsbock W, Bergmann M. Recurrent abscess after primary successful endo-sponge treatment of anastomotic leakage following

- rectal surgery. *World J Gastroenterol* 2010; **16**: 4570-4574 [PMID: 20857528 DOI: 10.3748/wjg.v16.i36.4570]
- 28 **Glitsch A**, von Bernstorff W, Seltrecht U, Partecke I, Paul H, Heidecke CD. Endoscopic transanal vacuum-assisted rectal drainage (ETVARD): an optimized therapy for major leaks from extraperitoneal rectal anastomoses. *Endoscopy* 2008; **40**: 192-199 [PMID: 18189215 DOI: 10.1055/s-2007-995384]
 - 29 **Kuehn F**, Janisch F, Schwandner F, Alsfasser G, Schiffmann L, Gock M, Klar E. Endoscopic Vacuum Therapy in Colorectal Surgery. *J Gastrointest Surg* 2016; **20**: 328-334 [DOI: 10.1007/s11605-015-3017-7]
 - 30 **Srinivasamurthy D**, Wood C, Slater R, Garner J. An initial experience using transanal vacuum therapy in pelvic anastomotic leakage. *Tech Coloproctol* 2013; **17**: 275-281 [PMID: 23111399 DOI: 10.1007/s10151-012-0911-9]
 - 31 **Blumetti J**, Chaudhry V, Prasad L, Abcarian H. Delayed transanal repair of persistent coloanal anastomotic leak in diverted patients after resection for rectal cancer. *Colorectal Dis* 2012; **14**: 1238-1241 [PMID: 22229958 DOI: 10.1111/j.1463-1318.2012.02932.x]
 - 32 **Brunner W**, Rossetti A, Vines LC, Kalak N, Bischofberger SA. Anastomotic leakage after laparoscopic single-port sigmoid resection: combined transanal and transabdominal minimal invasive management. *Surg Endosc* 2015; **29**: 3803-3805 [PMID: 25783831 DOI: 10.1007/s00464-015-4138-5]

P- Reviewer: Segre D, Tebala GD, Virk JS **S- Editor:** Qi Y
L- Editor: Stewart G **E- Editor:** Li D



Basic Study

Fibrinogen-thrombin collagen patch reinforcement of high-risk colonic anastomoses in rats

Juan Manuel Suárez-Grau, Carlos Bernardos García, Carmen Cepeda Franco, Cristina Mendez García, Salud García Ruiz, Fernando Docobo Durantez, Salvador Morales-Conde, Javier Padillo Ruiz

Juan Manuel Suárez-Grau, Department of General and Digestive Surgery, Riotinto Hospital, 21660 Huelva, Spain

Juan Manuel Suárez-Grau, Division of General and Laparoscopic Surgery, Clinic Quiron Sagrado Corazón, 41013 Seville, Spain

Juan Manuel Suárez-Grau, Institute of Biomedicine of Seville Research Center, University Hospital Virgen del Rocío, 41013 Seville, Spain

Carlos Bernardos García, Division of General Surgery, Hospital of San Juan de Dios, 41930 Bormujos, Spain

Carmen Cepeda Franco, Fernando Docobo Durantez, Salvador Morales-Conde, Javier Padillo Ruiz, Department of General and Digestive Surgery, University Hospital Virgen del Rocío, 41013 Seville, Spain

Cristina Mendez García, Department of General surgery, Hospital of Jerez, 11407 Jerez de la Frontera, Cadiz, Spain

Salud García Ruiz, Division of Surgery, Clinic Quiron Donostia, 20012 Donostia, Spain

Salvador Morales-Conde, Clinic Quiron Sagrado Corazón, 41013 Seville, Spain

Author contributions: Suárez-Grau JM and Bernardos García C wrote the paper; Suárez-Grau JM, Bernardos García C, Cepeda Franco C, Mendez García C and García Ruiz S performed the experiments and participated equally in treatment of animals; Suárez-Grau JM and Bernardos García C analyzed the data and reviewed the manuscript; Docobo Durantez F, Morales-Conde S and Padillo Ruiz J designed and coordinated the research.

Institutional review board statement: The appropriate approvals were obtained from the relevant Institutional Review Board of General and Digestive Surgery Department of University Hospital of Virgen del Rocío (Seville) and Riotinto Hospital (Huelva), as well as from the research ethics committee of both hospitals.

Institutional animal care and use committee statement: The study was approved by the Ethics Committee for experimental studies and experimental surgery Research Center, Institute of Biomedicine of Seville (IBIS). Animals were cared for at all times by qualified care professionals.

Conflict-of-interest statement: There is no conflict of interest in performing this study by either of the authors; material was donated by the Department of General and Digestive Surgery of Riotinto Hospital and Virgen del Rocío Hospital.

Data sharing statement: An independent statistical employee of the University Hospital of Virgen del Rocío performed the blinded data statistical analysis.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Juan Manuel Suárez-Grau, MD, PhD, Department of General and Digestive Surgery, Riotinto Hospital. Av. la Esquila, 5 Minas de Riotinto, 21660 Huelva, Spain. graugrau@gmail.com
Telephone: +34-62-9739398
Fax: +34-95-9252250

Received: January 18, 2016
Peer-review started: January 20, 2016
First decision: February 15, 2016
Revised: July 6, 2016
Accepted: July 20, 2016
Article in press: July 22, 2016
Published online: September 27, 2016

Abstract

AIM

To evaluate the effectiveness of human fibrinogen-thrombin collagen patch (TachoSil®) in the reinforcement of high-risk colon anastomoses.

METHODS

A quasi-experimental study was conducted in Wistar rats ($n = 56$) that all underwent high-risk anastomoses (anastomosis with only two sutures) after colectomies. The rats were divided into two randomized groups: Control group (24 rats) and treatment group (24 rats). In the treatment group, high-risk anastomosis was reinforced with TachoSil® (a piece of TachoSil® was applied over this high-risk anastomosis, covering the gap). Leak incidence, overall survival, intra-abdominal adhesions, and histologic healing of anastomoses were analyzed. Survivors were divided into two subgroups and euthanized at 15 and 30 d after intervention in order to analyze the adhesions and histologic changes.

RESULTS

Overall survival was 71.4% and 57.14% in the TachoSil® group and control group, respectively ($P = 0.29$); four rats died from other causes and six rats in the treatment group and 10 in the control group experienced colonic leakage ($P > 0.05$). The intra-abdominal adhesion score was similar in both groups, with no differences between subgroups. We found non-significant differences in the healing process according to the histologic score used in both groups ($P = 0.066$).

CONCLUSION

In our study, the use of TachoSil® was associated with a non-statistically significant reduction in the rate of leakage in high-risk anastomoses. TachoSil® has been shown to be a safe product because it does not affect the histologic healing process or increase intra-abdominal adhesions.

Key words: Colon; Rats; Anastomosis; Leak; TachoSil®; Surgery

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Anastomotic leakage is one of the most important complications in gastrointestinal surgery. We have performed a pioneering risk anastomosis procedure, carried out with a high risk of leakage, to test the use of thrombin and fibrinogen patch for the reinforcement and prevention of potential leakage. We obtained a significant reduction in the mortality rate without adding comorbidity. Patch application is simple and does not exceed operating time, and its use can be extremely helpful in emergency surgery or special situations that provide a high possibility of anastomosis dehiscence.

García C, García Ruiz S, Docobo Durantez F, Morales-Conde S, Padillo Ruiz J. Fibrinogen-thrombin collagen patch reinforcement of high-risk colonic anastomoses in rats. *World J Gastrointest Surg* 2016; 8(9): 627-633 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/627.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.627>

INTRODUCTION

Anastomotic leakage is a severe post-operative complication that can threaten a patient's life. It has a mean incidence in the published literature of 4%-8%, and its mortality can reach up to 22%^[1,2]. Several methods have been used to attempt to reduce anastomotic leakage associated with colonic surgery, with diverse results. As some authors have reported, staplers are the only method that maintains the incidence of anastomotic leakage under 10%^[3]. Other authors have used glues and tissue sealants to reinforce the suture. Cyanoacrylates and fibrin glues are most often used, with varying results in the literature; some studies state that the use of cyanoacrylates and fibrin sealants in this kind of surgery is both efficient and advantageous^[4,5], while others have failed to demonstrate such benefits^[6]. Few studies have analyzed other materials, such as TachoSil®, a human fibrinogen and thrombin patch. TachoSil® contains human fibrinogen, human thrombin, and the following excipients: Equine collagen, human albumin, riboflavin (E101), sodium chloride, sodium citrate (E331), and L-arginine-hydrochloride. TachoSil® is indicated in adults as a supportive treatment in surgery for the improvement of hemostasis, the promotion of tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient. Experimental studies have tried to assess if this product can improve the results of colonic anastomoses, with diverse results^[7-10]. An important aspect of this topic is the definition of high-risk anastomoses. Tebala *et al*^[5] defined this kind of anastomoses as including emergency surgery, ischemic or inflammatory tissues, esophagus or extraperitoneal rectus, and immunosuppression.

We hypothesized that colonic anastomosis carried out under poor conditions can be improved with the use of TachoSil® by decreasing anastomotic leakage and its complications.

MATERIALS AND METHODS

Study design

A prospective, comparative, semi-experimental study in animals was conducted to analyze the effects of the application of a human fibrinogen-thrombin patch (TachoSil®) over high-risk anastomosis sites. The hypothesis was that this product would decrease the incidence and severity of colonic leakage. We compared the results with a control group in which there was only high-risk anastomosis. The study was carried out under the conditions established by the Helsinki statement,

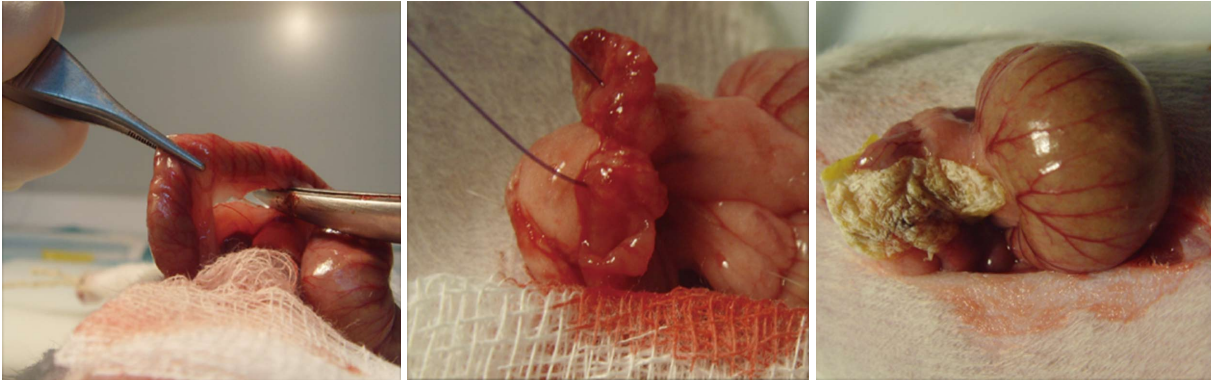


Figure 1 Surgical technique.

Table 1 Adhesive score

Adhesive score
0: No adhesions
1: Extremely soft adhesions
2: Stronger adhesions, but dissectible with dull dissection
3: Stronger adhesions only dissectible with sharpen tools
4: Stenosis

which regulates the terms and conditions for animal experiments. There was no competing interest for any of the authors. The authors did not receive any grant or sponsorship for this study. Materials were donated by the Department of Surgery of the University Hospital of Virgen del Rocío and Riotinto Hospital.

Animals

This study was performed on 56 white Wistar rats of both sexes weighing between 250 g and 350 g. Animals were divided into two groups (control group and treatment group), each consisting of 28 individuals. High-risk anastomosis was performed in all rats. A piece of fibrinogen-thrombin sealant was added that covered the entire anastomosis site in the treatment group.

Technical procedure

Anesthesia was induced with intraperitoneal ketamine (20 mg/kg), after which a laparotomy was performed. We then performed a partial colectomy of 2-3 cm just after the cecum, which was closed with an anastomosis with only two stitches of 4-0 monocryl in the mesenteric and anti-mesenteric borders of the colon. In addition, a 2 cm × 2 cm piece of TachoSil® was applied over the anastomosis, with light compression using small, wet gauze in the treatment group. Each piece was lightly wetted with 0.9% saline. The gauze was gently removed and the anastomosis site checked after 5 min to ensure the TachoSil® was in the proper location. The laparotomy was closed with 3-0 vicryl suture in a simple continuous suture for the muscle plane and 3-0 silk in a simple interrupted suture for the skin (Figure 1).

The early deceased animals underwent necropsy in order to establish the cause of death. The survivors

were euthanized at 15 and 30 d post-operatively after a randomized process. During necropsy, the formation of intra-abdominal adhesions was quantified with a numeric scale (Table 1) to compare both groups at 15 and 30 d post-operatively. In all animals, colonic anastomosis was retrieved to analyze the histopathologic healing process according to the Biert scheme (Table 2), which analyzed nine parameters. The histologic analysis, using hematoxylin and eosin staining, was performed by a pathologist blinded for the two groups.

Statistical analysis

The program used for statistical analysis was SPSS v16 for Windows, and the statistical review was performed by a biomedical statistician. Numerical results were analyzed using means and standard deviations. The Kaplan-Meier method was used to assess survival. Leakage incidence was analyzed with the χ^2 test for dichotomous variables. The intra-abdominal adhesion score was compared between groups with the Mann-Whitney test, as the variable was qualitative. The histopathologic healing process was analyzed with the Student's *t*-test, with sub-analysis performed with the Mann-Whitney test when necessary. A *P* value < 0.05 was considered significant.

RESULTS

Survival and leakage incidence

The number of events, defined as death as a consequence of colonic leakage, was 10 (35.7%) in the control group and 6 (21.4%) in the TachoSil® group. All deaths happened before the fourth post-operative day. Four animals in both groups died due to other causes, namely hemorrhage, post-anesthesia and bowel obstruction, with no relation to the experimental study. The mean survival per group was 19.5 ± 2.6 (control) and 23.7 ± 2.2 d (TachoSil®). With these results, the overall survival was 57.14% and 71.4% in the control and TachoSil® groups, respectively (*P* = 0.29) (Figure 2), with no significant differences between the groups.

Intra-abdominal adhesions

The results are shown in Table 3. We performed com-

Table 2 Histopathologic Biert' scheme

Parameters	Score			
	0	1	2	3
Necrosis	No	Small patches	Large patches	Massive
PMNs	Normal	Slightly increased	Strong infiltration	Massive infiltration
Lymphocytes	Normal	Slightly increased	Strong infiltration	Massive infiltration
Macrophages	Normal	Slightly increased	Strong infiltration	Massive infiltration
Edema	No	Slight	Strong	Massive
Epithelium	Glandular normal	Cubic normal	Cubic incomplete	Absent
Submucosa-muscular	Good bridges	Mild bridges	Few bridges	Bridges absent
Angiogenesis	Extensive	Strong	Slight	Absent
Fibrosis	Extensive	Strong	Slight	Absent

PMNs: Polymorphonuclear cells.

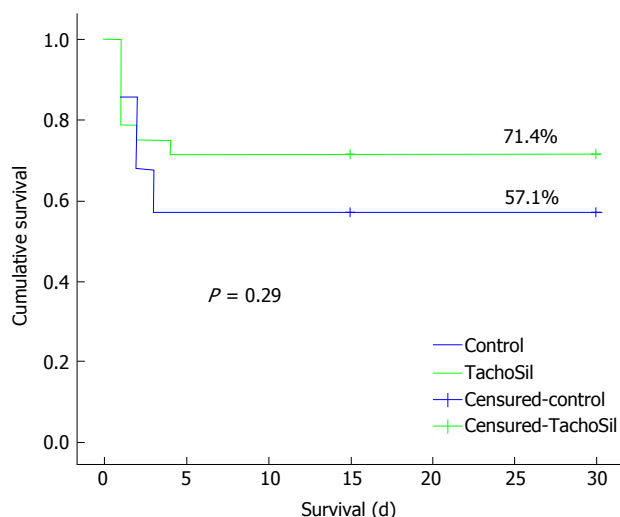
Table 3 Intra-abdominal adhesion score in surviving animals

	Mann-Whitney mean ranges	P value
Survivors (15 d vs 30 d)	25.11 vs 11.12	0.0012
Control (15 d vs 30 d)	10.53 vs 5.5	0.017
TachoSil (15 d vs 30 d)	14.75 vs 6.25	0.001
Control vs TachoSil (15 d)	9.5 vs 10.45	0.685
Control vs TachoSil (30 d)	9.71 vs 8.50	0.584

Table 4 Most relevant parameters in histopathologic analysis (mean \pm SD)

	Control	TachoSil	P value
PMNs	0.21 \pm 0.42	0.78 \pm 0.64	0.010
Macrophages	0.50 \pm 0.65	0.89 \pm 0.47	0.026
Edema	0.43 \pm 0.64	0.94 \pm 0.63	0.017
Epithelium regeneration	0.64 \pm 0.92	1.11 \pm 0.58	0.031

PMNs: Polymorphonuclear cells.

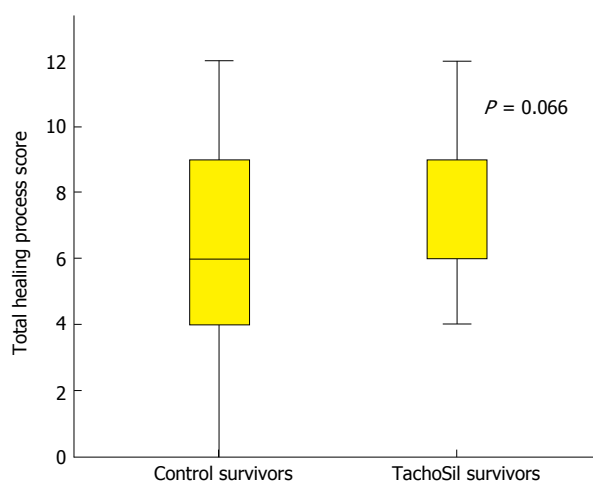
**Figure 2** Survival in both groups.

parisons according to both the time (15 d vs 30 d) and group [control (16 rats) vs TachoSil® (20 rats)]. Distribution of animals sacrificed: control-15 d = 9 rats, control-30 d = 7 rats; TachoSil-7 d = 10 rats, TachoSil-15 d = 10 rats. The adhesion score was significantly different when comparing all groups according to the time, showing a much better score in animals euthanized at day 30. However, no differences were found at day 15 or day 30 when comparing groups.

Histopathologic healing process

Healing of the anastomoses was analyzed following the Biert scheme. The global results are shown in Figures 3 and 4.

Only four parameters (Table 4) showed significant

**Figure 3** Healing of the anastomoses in both groups.

differences between the control and TachoSil® groups with the Student's *t*-test, and were always worse in the TachoSil® group polymorphonuclear cells 0.21 \pm 0.42 vs 0.78 \pm 0.64, *P* = 0.01; macrophages 0.50 \pm 0.65 vs 0.89 \pm 0.47, *P* = 0.026; oedema 0.43 \pm 0.64 vs 0.94 \pm 0.63, *P* = 0.017; and epithelium regeneration 0.64 \pm 0.92 vs 1.11 \pm 0.58, *P* = 0.031. The rest of parameters were similar between groups.

When we applied the total score for this analysis, defined as the sum of all values of each parameter, we found nearly significant differences between groups. Among all survivors, the control group had a mean total healing score of 6.21 \pm 3.21, whereas the TachoSil® group had a mean of 8 \pm 2.05 (*P* = 0.066) (Figure 3).

Sub-analysis of this total healing process score accord-

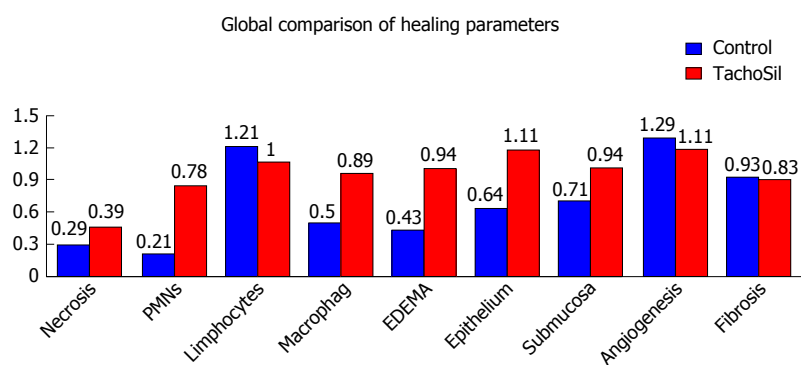


Figure 4 Global comparison of healing parameters. PMNs: Polymorphonuclear cells.

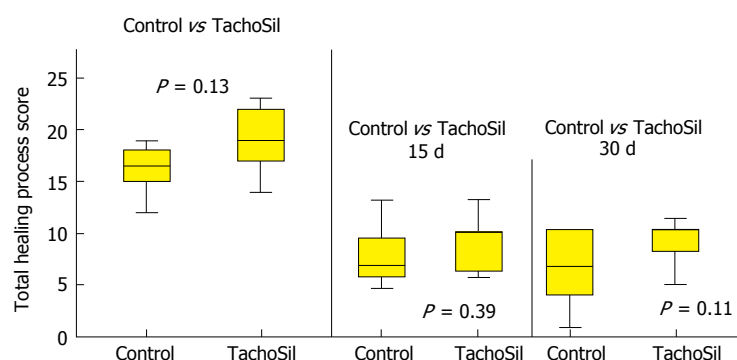


Figure 5 Healing process scores at 15 d and 30 d, and global analysis in surviving animals.

ing to the post-operative day (15 and 30 d) did not show statistically significant differences, but we did see a trend towards a worsened healing process in the TachoSil® group, especially at the end of the period. On days 15 and 30, the results were 7.5 vs 9.5 ($P = 0.39$) and 6.17 vs 9.9 ($P = 0.112$) in the control group vs the TachoSil® group, respectively (mean ranges) (Figure 5). There were no differences when the analysis was performed between groups (global analysis) (7.15 vs 10.75; $P = 0.13$).

DISCUSSION

Colonic anastomosis failure can be a life threatening complication following colonic surgery. Over time, great efforts have been made to improve the results of this procedure and define the risk factors for anastomosis failure^[1,2,11]. Systemic factors (such as diabetes and steroid use) and local factors (such as radiotherapy and tension or hemorrhage in the suture) can lead to a poor result in the healing process of the colon^[12-14]. The period in which a leak occurs is usually between days 5 and 6 post-operation. Before this period, the strength of anastomosis is mainly held by the suture, but after day 5 or 6 the healing process of the colonic wall, especially with regards to the collagen formation, is most important, as the suture material loses efficacy at that time. A variety of products^[6,15-19] have been used to reinforce intestinal anastomoses (e.g., cyanoacrylate, fibrin sealants, amniotic, collagen and dura mater membranes, and mechanical staplers), all with different results. The application of a

fibrinogen and thrombin patch over colonic anastomoses is a relatively new idea^[7]. Some authors^[19,20] used the classical cecal puncture model to define high-risk anastomosis, thereby providing the sepsis model^[20-24]. To date, there has not been any consensus regarding the definition of high-risk anastomosis and, to our knowledge, there have been few studies that have examined the application of TachoSil® over colonic anastomoses^[7-10,20-24], with only one carried out using a high-risk anastomosis^[10]. Although these studies showed the method to be safe and feasible, some results have been controversial; Ozel *et al*^[7] showed that this product increased the inflammatory reaction and led to a worsened healing process with less mechanical strength. In contrast, Stumpf *et al*^[9] found that it led to a better histopathologic healing process as a consequence of the decrease in suture material in the anastomotic line and that a suture-free anastomosis is reliable. Norden-toft *et al*^[8,22] studied this product applied over normal small-bowel anastomoses and found no differences in the mechanical strength, degree of stenosis, or healing process, with the incidence of anastomotic leakage also being similar between groups. In our study, we noted an evident reduction of anastomotic leakage incidences (31.7% vs 21.4% in control and TachoSil® groups, respectively), but these differences were not significant ($P = 0.29$). Even when a potentially injurious agent such as 5-fluorouracil is used, it has been verified that applying anastomosis TachoSil® confers greater resistance by acting as a protective agent^[24]. In a study using mice, Pantelis *et al*^[10] achieved a statistically significant difference in

the lethality and leakage rates in the group that received TachoSil®, as well as finding that its use did not increase the formation of intra-abdominal adhesions. They did not find any differences between groups. In studies that analyzed the use of TachoSil® in bowel anastomoses, Nordentoft *et al*^[8] reported no differences between groups. In contrast, Ozel *et al*^[7] noted that TachoSil® increased the formation of peri-anastomotic adhesions. Regarding the histopathologic healing process, we found neither advantages nor disadvantages when TachoSil® was applied. However, when we analyzed this process with both individual and global scores, some individuals were statistically different with regards to group (control or treatment), but when the global score was compared, no differences were observed. Some authors, such as Ozel, affirmed that if TachoSil® is used, the neutrophilic granulocyte count can increase, and this carries a worsened prognosis for healing as a result of excessive metalloproteinases. These results were also observed by van der Ham *et al*^[21]. In contrast, Pantelis observed that if TachoSil® is applied in high-risk anastomosis, an improvement in the healing process can be observed. In our study, the healing process is exacerbated and inflammatory parameters were increased when TachoSil® was used, compared to the control group. However this does not affect the creation of useful anastomosis, only higher growth of tissue in the area where it is applied, accompanied by obvious signs of inflammation. This has not affected the result of the study and the rate of leakage has decreased, therefore we believe that a stronger healing process is useful in reinforcing the consistency of anastomosis.

We think that, despite the worsened healing in some individual parameters in the TachoSil® group, the improvement in leak incidence can be explained by the sealant effect of the collagen patch (*i.e.*, the mechanical sealant achieved by this sponge, which is a well-established effect of this product)^[7,8,23].

In conclusion, our study showed that the application of TachoSil® led to a non-statistically significant decrease in both mortality and anastomotic leakage rates. Furthermore, the use of this product did not affect the histopathologic healing process or increase the formation of adhesions, and so it can be regarded as a very safe product. We focused on the importance of the mechanical effect of TachoSil® in sealing the anastomosis gap. The use of TachoSil® is not justified in routine colonic surgery due to the low colonic anastomotic leakage rates in those procedures. Although we demonstrated that TachoSil® does not decrease the complication rate in high-risk anastomoses, based on the controversial data existing in the literature, we recommend that clinical studies should be performed to clarify this topic, as it may have potentially important effects in surgery.

anastomosis in rats. The hypothesis to be tested is decreasing anastomotic leaks using this product. The triple-blind comparative results confirm a decrease in leakage anastomotic.

Research frontiers

The main frontier of the study is the reduction of anastomosis leakage in anastomosis with risk factors.

Innovations and breakthroughs

Decreasing the rate of leaks in anastomosis using an absorbable sheet on the anastomosis when the procedure was performed in high-risk conditions.

Applications

The results can be applied in digestive surgery (*i.e.*, intestinal and colorectal anastomosis), especially in emergency surgeries and patients with high comorbidities.

Peer-review

This manuscript showed the potential application of TachoSil® in colonic sutures after surgery. The study was straight-forward and rational. The application apparently has some merits.

REFERENCES

- 1 **Matthiessen P**, Hallböök O, Rutegård J, Simert G, Sjö Dahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann Surg* 2007; **246**: 207-214 [PMID: 17667498 DOI: 10.1097/SLA.0b013e3180603024]
- 2 **Matthiessen P**, Hallböök O, Andersson M, Rutegård J, Sjö Dahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. *Colorectal Dis* 2004; **6**: 462-469 [PMID: 15521937 DOI: 10.1111/j.1463-1318.2004.00657.x]
- 3 **Smith LE**. Anastomosis with EEA stapler after anterior colonic resection. *Dis Colon Rectum* 1981; **1**: 160-167 [DOI: 10.1007/bf02641867]
- 4 **Coover HW**, Joyner FB, Sheareer NH, Wicner TH. Chemistry and performance of cyanoacrylate adhesive. *J Soc Plast Enf* 1959; **15**: 413-417
- 5 **Tebala GD**, Ceriati F, Ceriati E, Vecchioli A, Nori S. The use of cyanoacrylate tissue adhesive in high-risk intestinal anastomoses. *Surg Today* 1995; **25**: 1069-1072 [PMID: 8645945 DOI: 10.1007/BF00311697]
- 6 **Nursal TZ**, Anarat R, Bircan S, Yildirim S, Tarim A, Haberal M. The effect of tissue adhesive, octyl-cyanoacrylate, on the healing of experimental high-risk and normal colonic anastomoses. *Am J Surg* 2004; **187**: 28-32 [PMID: 14706582 DOI: 10.1016/j.amjsurg.2003.02.007]
- 7 **Ozel SK**, Kazez A, Akpolat N. Does a fibrin-collagen patch support early anastomotic healing in the colon? An experimental study. *Tech Coloproctol* 2006; **10**: 233-236 [PMID: 16969611 DOI: 10.1007/s10151-006-0285-y]
- 8 **Nordentoft T**, Rømer J, Sørensen M. Sealing of gastrointestinal anastomoses with a fibrin glue-coated collagen patch: a safety study. *J Invest Surg* 2007; **20**: 363-369 [PMID: 18097878 DOI: 10.1080/08941930701772173]
- 9 **Stumpf M**, Junge K, Rosch R, Krone C, Klinge U, Schumpelick V. Suture-free small bowel anastomoses using collagen fleece covered with fibrin glue in pigs. *J Invest Surg* 2009; **22**: 138-147 [PMID: 19283617 DOI: 10.1080/08941930802713001]
- 10 **Pantelis D**, Beissel A, Kahl P, Wehner S, Vilz TO, Kalf J. The effect of sealing with a fixed combination of collagen matrix-bound coagulation factors on the healing of colonic anastomoses in experimental high-risk mice models. *Langenbecks Arch Surg* 2010; **395**: 1039-1048 [PMID: 20680329 DOI: 10.1007/s00423-010-0703-5]
- 11 **Peeters KC**, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, Rutten HJ, van de Velde CJ. Risk factors for

COMMENTS

Background

This is an experimental study to test the absorbable product TachoSil® in risk

- anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005; **92**: 211-216 [PMID: 15584062 DOI: 10.1002/bjs.4806]
- 12 **Tagart RE**. Colorectal anastomosis: factors influencing success. *J R Soc Med* 1981; **74**: 111-118 [PMID: 7009860]
 - 13 **Goligher JC**, Graham NG, De Dombal FT. Anastomotic dehiscence after anterior resection of rectum and sigmoid. *Br J Surg* 1970; **57**: 109-118 [PMID: 5467147 DOI: 10.1002/bjs.1800570208]
 - 14 **Daly JM**, Vars HM, Dudrick SJ. Effects of protein depletion on strength of colonic anastomoses. *Surg Gynecol Obstet* 1972; **134**: 15-21 [PMID: 5007170]
 - 15 **Eryilmaz R**, Samuk M, Tortum OB, Akcakaya A, Sahin M, Goksel S. The role of dura mater and free peritoneal graft in the reinforcement of colon anastomosis. *J Invest Surg* 2007; **20**: 15-21 [PMID: 17365403 DOI: 10.1080/08941930601126108]
 - 16 **Schreinemacher MH**, Bloemen JG, van der Heijden SJ, Gijbels MJ, Dejong CH, Bouvy ND. Collagen fleeces do not improve colonic anastomotic strength but increase bowel obstructions in an experimental rat model. *Int J Colorectal Dis* 2011; **26**: 729-735 [PMID: 21344301 DOI: 10.1007/s00384-011-1158-z]
 - 17 **Elemen L**, Sarimurat N, Ayik B, Aydin S, Uzun H. Is the use of cyanoacrylate in intestinal anastomosis a good and reliable alternative? *J Pediatr Surg* 2009; **44**: 581-586 [PMID: 19302863 DOI: 10.1016/j.jpedsurg.2008.08.033]
 - 18 **Nandakumar G**, Richards BG, Trencheva K, Dakin G. Surgical adhesive increases burst pressure and seals leaks in stapled gastro-jejunostomy. *Surg Obes Relat Dis* 2010; **6**: 498-501 [PMID: 20176513 DOI: 10.1016/j.soard.2009.11.016]
 - 19 **Byrne DJ**, Hardy J, Wood RA, McIntosh R, Hopwood D, Cuschieri A. Adverse influence of fibrin sealant on the healing of high-risk sutured colonic anastomoses. *J R Coll Surg Edinb* 1992; **37**: 394-398 [PMID: 1491373]
 - 20 **Uludag M**, Citgez B, Ozkaya O, Yetkin G, Ozcan O, Polat N, Isgor A. Effects of amniotic membrane on the healing of normal and high-risk colonic anastomoses in rats. *Int J Colorectal Dis* 2009; **24**: 809-817 [PMID: 19280199 DOI: 10.1007/s00384-009-0691-5]
 - 21 **van der Ham AC**, Kort WJ, Weijma IM, van den Ingh HF, Jeekel J. Effect of fibrin sealant on the healing colonic anastomosis in the rat. *Br J Surg* 1991; **78**: 49-53 [PMID: 1998864 DOI: 10.1002/bjs.1800780117]
 - 22 **Nordentoft T**. Sealing of gastrointestinal anastomoses with fibrin glue coated collagen patch. *Dan Med J* 2015; **62**: pii: B5081 [PMID: 26050838]
 - 23 **Tallón-Aguilar L**, Lopez-Bernal Fde A, Muntane-Relat J, García-Martínez JA, Castillo-Sánchez E, Padillo-Ruiz J. The use of TachoSil as sealant in an experimental model of colonic perforation. *Surg Innov* 2015; **22**: 54-60 [PMID: 24902692 DOI: 10.1177/1553350614535853]
 - 24 **Sabino FD**, Campos CF, Caetano CE, Trotte MN, Oliveira AV, Marques RG. Effects of TachoSil and 5-fluorouracil on colonic anastomotic healing. *J Surg Res* 2014; **192**: 375-382 [PMID: 24976442 DOI: 10.1016/j.jss.2014.05.067]

P- Reviewer: Kok VC, Tomizawa M **S- Editor:** Gong ZM

L- Editor: Rutherford A **E- Editor:** Li D



Retrospective Study

Total pancreatectomy: Short- and long-term outcomes at a high-volume pancreas center

Hazem M Zakaria, John A Stauffer, Massimo Raimondo, Timothy A Woodward, Michael B Wallace, Horacio J Asbun

Hazem M Zakaria, Department of Hepatopancreatobiliary and Liver Transplantation Surgery, National Liver Institute, Menoufia University, Al-Minufya 22732, Egypt

John A Stauffer, Horacio J Asbun, Department of Surgery, Mayo Clinic, Jacksonville, FL 32224, United States

Massimo Raimondo, Timothy A Woodward, Michael B Wallace, Department of Gastroenterology, Mayo Clinic, Jacksonville, FL 32224, United States

Author contributions: Zakaria HM contributed to the conception and design of the study, collection, analysis and interpretation of data, drafting and critical revision of the article, and generation/collection of figures; Stauffer JA contributed to the conception and design of the study, experiments, collection, analysis and interpretation of data, drafting and critical revision of the article and generation/collection of figures; Raimondo M, Woodward TA and Wallace MB contributed to the conception and design of the study, experiments, collection of data and critical revision of the article; Asbun HJ contributed to the conception and design of the study, experiments, collection, analysis and interpretation of data, drafting and critical revision of the article and generation/collection of figures; all authors gave final approval of the article.

Institutional review board statement: We conducted a retrospective study of 103 patients who underwent TP between March 1995 and December 2014 at Mayo Clinic in Jacksonville, Florida using data collected from an institutional review board-approved prospective database.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient gave informed consent for institutional data collection and sharing.

Conflict-of-interest statement: Dr. Zakaria, Dr. Stauffer, Dr. Raimondo, Dr. Woodward, Dr. Wallace and Dr. Asbun report no biomedical financial interests or potential conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: John A Stauffer, MD, Associate Professor of Surgery, Department of Surgery, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States. stauffer.john@mayo.edu
Telephone: +1-904-9532214
Fax: +1-904-9537368

Received: March 17, 2016
Peer-review started: March 20, 2016
First decision: April 19, 2016
Revised: May 3, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: September 27, 2016

Abstract

AIM

To identify the current indications and outcomes of total pancreatectomy at a high-volume center.

METHODS

A single institutional retrospective study of patients undergoing total pancreatectomy from 1995 to 2014 was performed.

RESULTS

One hundred and three patients underwent total

pancreatectomy for indications including: Pancreatic ductal adenocarcinoma ($n = 42$, 40.8%), intraductal papillary mucinous neoplasms ($n = 40$, 38.8%), chronic pancreatitis ($n = 8$, 7.8%), pancreatic neuroendocrine tumors ($n = 7$, 6.8%), and miscellaneous ($n = 6$, 5.8%). The mean age was 66.2 years, and 59 (57.3%) were female. Twenty-four patients (23.3%) underwent a laparoscopic total pancreatectomy. Splenic preservation and portal vein resection and reconstruction were performed in 24 (23.3%) and 18 patients (17.5%), respectively. The 90 d major complications, readmission, and mortality rates were 32%, 17.5%, and 6.8% respectively. The 1-, 3-, 5-, and 7-year survival for patients with benign indications were 84%, 82%, 79.5%, and 75.9%, and for malignant indications were 64%, 40.4%, 34.7% and 30.9%, respectively.

CONCLUSION

Total pancreatectomy, including laparoscopic total pancreatectomy, appears to be an appropriate option for selected patients when treated at a high-volume pancreatic center and through a multispecialty approach.

Key words: Intraductal papillary mucinous neoplasms; Laparoscopic total pancreatectomy; Pancreatic ductal adenocarcinoma; Laparoscopy; Pancreas cyst; Pancreas cancer

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Treatment by total pancreatectomy for diseases of the pancreas has been gained acceptance and used more frequently by pancreatic surgeons. This review highlights a large volume single institutional experience with this operation demonstrating acceptable short-term and long-term outcomes.

Zakaria HM, Stauffer JA, Raimondo M, Woodward TA, Wallace MB, Asbun HJ. Total pancreatectomy: Short- and long-term outcomes at a high-volume pancreas center. *World J Gastrointest Surg* 2016; 8(9): 634-642 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/634.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.634>

INTRODUCTION

In selected patients, total pancreatectomy (TP) has been established as a potential option in the treatment of pancreatic ductal adenocarcinoma (PDAC), invasive or diffuse intraductal papillary mucinous neoplasms (IPMN), multiple pancreatic neuroendocrine tumors (PNET)^[1-4]. TP is still also one of the treatment modalities in chronic pancreatitis with severe pain, pancreatic fistula or hemorrhage after pancreaticoduodenectomy (PD)^[3,5-7]. Improvement in postoperative management, including better pancreatic enzyme formula, long-acting insulin, and autologous islet cell transplantation, has made TP

a viable choice in the treatment of different pancreatic diseases^[8,9].

Although TP is performed at an increasing rate at major pancreatic centers, there is still debate regarding its indications and outcomes^[2-4]. This study aimed to analyze the indications and short- and long-term outcomes of TP in the spectrum of pancreatic resections in our high-volume center.

MATERIALS AND METHODS

We conducted a retrospective study of 103 patients who underwent TP between March 1995 and December 2014 at Mayo Clinic in Jacksonville, Florida using data collected from an institutional review board-approved prospective database.

The preoperative data, including demographic data and clinical picture, operative details, and postoperative data were collected and analyzed.

Operative strategy

The American Society of Anesthesiologists classification^[10] and Eastern Cooperative Oncology Group performance status^[11] were used for evaluation of the preoperative risk. All patients were optimized medically prior to surgery.

TP was performed either open or laparoscopic. It was done as pylorus-preserving, standard, or completion TP (of previous distal pancreatectomy or PD). The operation was done with and without splenectomy.

In cases with partial resection in pancreatic tumors, the specimen margin was analyzed by frozen section. The procedure was converted to TP if the margins showed carcinoma *in situ* or invasive carcinoma. TP was not performed for frozen section findings of moderate dysplasia or adenomatous changes at the margin. International consensus guidelines for the management of patients diagnosed with IPMN was used throughout the study time period, as appropriate. Guidelines from 2006^[12] were followed up until these were updated in 2012^[13].

The International Study Group of Pancreatic Surgery (ISGPS) classification of venous resection was used as follows^[14]: Type I: Partial venous resection with direct closure (venorrhaphy); Type II: Partial venous excision with closure by patch graft; Type III: Excision with primary end to end venous anastomosis; Type IV: Venous resection with interposition venous graft.

Histopathological data on pancreatic tumor staging were collected according to the tumor, node and metastases staging system. IPMN pathology was defined as per World Health Organization criteria into 4 categories based upon the degree of dysplasia: Adenoma, border line (low-moderate dysplasia), carcinoma *in situ* (CIS) high-grade dysplasia, or invasive carcinoma^[2]. PDAC without IPMN was considered to be de novo, but PDAC associated with IPMN was considered to be arisen from these IPMN.

Postoperative complications occurring in the first 90 d

Table 1 Demographics for 103 patients undergoing total pancreatectomy with subgroup analysis

Variable	Overall (n = 103)	PDAC (n = 42)	IPMN (n = 40)	LTP (n = 24)
Age, yr ¹	70.2 (32-84.5)	70.3 (33.3-84.5)	71.3 (42.9-81.1)	70.3 (37.3-84.5)
Body mass index ¹	25.1 (17.7-42.1)	24.2 (17.7-39.8)	25.8 (18.5-42.1)	26.7 (17.7-36.3)
Male	44 (42.7%)	18 (42.9%)	19 (47.5%)	13 (54.2%)
Hypertension	70 (68%)	29 (69%)	31 (77.5%)	14 (58.3%)
Diabetes	46 (44.7%)	19 (45.2%)	16 (40%)	13 (54.2%)
Cardiac disease	31 (30.1%)	8 (19%)	14 (35%)	7 (29.2%)
Pulmonary disease	19 (18.4%)	7 (16.7%)	7 (17.5%)	5 (20.8%)
ASA				
II	24 (23.3%)	11 (26.2%)	9 (22.5%)	2 (8.3%)
III	72 (69.9%)	26 (61.9%)	29 (72.5%)	22 (91.7%)
IV	7 (6.8%)	5 (11.9%)	2 (5%)	0
Type of resection				
Standard	35 (34%)	17 (40.5%)	10 (25%)	5 (20.8%)
Pylorus preserving	56 (54.4%)	20 (47.6%)	27 (67.5%)	16 (66.7%)
Completion	12 (11.6%)	5 (11.9%)	3 (7.5%)	3 (12.5%)

¹Values are median (range), values in parenthesis are percentages unless otherwise indicated. ASA: American Society of Anesthesiologists score; IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy; PDAC: Pancreatic ductal adenocarcinoma.

after surgery were graded from (0 to 5) according to the Clavien system^[15]. Grade I and II complications were considered minor and Grade III, IV and V were considered major complications. International consensus guidelines were used to evaluate specific complications^[16,17]. Major glycemic events included complications or readmissions related to severe hyperglycemia or hypoglycemia. Cardiac complications, pulmonary complications, renal insufficiency, or hepatic insufficiency were defined as temporary organ system dysfunction requiring supportive care over the usual standard postoperative measures.

The follow-up period (1-18 years) was from date of surgery. Any death during the hospital stay or within the first 90 d after surgery was defined as perioperative mortality. Readmissions to any facility were recorded for 90 d after surgery.

After analysis of results and outcomes from our previous publication in 2009^[4], patients undergoing consideration for total pancreatectomy were sent for preoperative evaluation and counseling by a nutrition and endocrine team for the anticipated exocrine and endocrine insufficiency caused by surgical intervention. Postoperatively, patients were seen and followed in the hospital setting by the inpatient nutrition and endocrine team for ongoing education and management regarding the subsequent pancreatic insufficiency. Insulin and enzyme replacement were determined according to individual patient needs. In addition, percutaneous jejunostomy feeding tube placement became a standard procedure during TP after 2009, and many patients were started on enteral tube feeds in the hospital setting and continued on after discharge to aid in avoiding readmissions for malnutrition.

Postoperatively, patients were treated on the medical-surgical floor and intensive care use was not routine unless indicated. Perioperative use of parenteral nutrition and blood product transfusion was also limited unless indicated. Based on final pathology, adjuvant

treatments including chemotherapy or radiotherapy were recommended to patients undergoing TP for periampullary adenocarcinoma.

Statistical analysis

Data were collected and analyzed by a biomedical statistician using SPSS version 21.0 (SPSS Inc., Chicago, IL, United States). A Kaplan-Meier curve was used for the analysis of survival.

RESULTS

From March 1995 to December 2014, 983 pancreatic resections were performed for benign and malignant pancreatic diseases; TP was performed in 103 patients (10.5%). The demographic and preoperative clinicopathological data are listed in Table 1. Subgroup analysis for those undergoing TP for PDAC and IPMN is shown. Indications for TP (rather than partial pancreatectomy) was multifocal disease (55 patients, 53.4%), positive margins (23 patients, 22.3%), elective completion TP for recurrence of the primary pathology (5 patients, 4.9%), or other (20 patients, 19.4%). There were no cases with emergent TP as treatment for postoperative pancreatic fistula (POPF) or hemorrhage from patients undergoing partial pancreatectomy in this study. POPF was treated with interventional radiological procedures, and in this study, all completion TP was performed in an elective fashion for pancreatic pathology.

Overall, 79 patients (76.7%) underwent an open TP. Laparoscopic TP (LTP) was attempted in 31 patients (30.1%), and conversion to open occurred in 7 patients (22.6%) due to adhesions from chronic pancreatitis in 5 patients, bleeding in 1 patient, and portal vein involvement by the tumor in 1 patient. Of the 24 patients who did not require conversion from LTP, a hand-assisted approach was used for 2 patients, and subgroup analysis is given in the tables. LTP was introduced in November

Table 2 Operative variables for 103 patients undergoing total pancreatectomy with subgroup analysis

Variable	Overall (n = 103)	PDAC (n = 42)	IPMN (n = 40)	LTP (n = 24)
Operative time (min) ¹	426 (165-930)	390 (165-636)	435 (240-930)	534 (234-770)
Estimated blood loss (mL) ¹	500 (50-18000)	500 (50-7800)	525 (50-18000)	200 (50-600)
Intraoperative pRBC transfusion (unit) ¹	1 (0%-40%)	2 (0%-30%)	1 (0%-40%)	0 (0%-2%)
Vein resection	18 (17.5%)	13 (40%)	4 (10%)	1 (4.2%)

¹Values are median (range), values in parenthesis are percentages unless otherwise indicated. IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy; PDAC: Pancreatic ductal adenocarcinoma; pRBC: Intraoperative packed red blood cell.

2008, and a total of 52 patients (50.5%) had TP after this date. Of these, 28 (53.8%) underwent open surgery and 24 (46.2%) underwent LTP. Spleen-preserving TP was done in 29 patients (28.2%), four of whom underwent spleen-preserving LTP.

Operative variables are found in Table 2. LTP was found to have longer operative times, but less blood loss. Vein resection was performed in 18 patients (17.5%). The resections were conducted according to the ISGPS classification of vein resection, which included type I (lateral venorrhaphy) in 4 patients (22.22%), type II (patch graft) in 2 (11.11%; 1 from gonadal vein and 1 from bovine graft), type III (primary anastomosis) in 6 (33.33%), and type IV (interposition venous graft) in 6 (33.33%; 4 by 14 mm polytetrafluoroethylene synthetic graft, 1 from gonadal vein, and 1 from splenic vein). One patient of LTP had venous resection and laparoscopic lateral venorrhaphy.

Table 3 gives the 90-d complications and postoperative outcomes, including length of stay and readmission rate, for those undergoing TP overall and by subgroup. Major postoperative complications were found in 33 (32%) patients, and reoperation was done for 7 patients (6.8%) due to abdominal collections (4 patients), post-pancreatectomy hemorrhage (2 patients), and intestinal fistula not responding to conservative or radiological interventions (1 patient).

Pathological indications for TP are listed in Table 4. PDAC and IPMN were the most common indications for surgery. Sixty-two patients (60.2%) were found to have IPMN upon final pathology. Forty patients (38.8%) had this as the only pathologic process, while IPMN was associated with other pancreatic pathology in 22 patients (21.4%).

Twenty of 42 patients with PDAC (47.6%), had tumor recurrence; 10 (50%) had distant metastasis (mainly to the liver and lung), 3 (15%) local recurrence, and 7 (35%) had both distant and local recurrence. The mean time of recurrence was 9.5 mo (range: 2.5-27 mo).

Overall, the 90-d perioperative mortality was 7 patients (6.8%). The 1-, 3-, 5-, and 7-year total survival rate for all 103 patients were 73.7%, 61.3%, 57.5%, and 53.8%, respectively (Figure 1A). The 1-, 3-, 5-, and 7-year survival for patients without malignant tumors (50 patients) were 84%, 82%, 79.5%, and 75.9%, respectively, while in patients with malignant findings (53 patients) the survival rates were 64%, 40.4%, 34.7%,

and 30.9%, respectively. The 1-, 3-, 5-, and 7-year survival rates in patients who had PDAC (42 patients) were 59.5%, 29.2%, 21.9%, and 18.3%, respectively (Figure 1B).

The 1-, 3-, 5-, and 7-year survival rates in patients with non-invasive IPMN (44 patients) were 84.1%, 76.9%, 73.8%, and 70.1%, respectively, while in patients with invasive IPMN (18 patients) the survival rates were 77.8%, 44.8%, 37.3%, and 29.8%, respectively.

DISCUSSION

Enthusiasm for TP has varied with time. This major operation should be assessed carefully for operative risk and postoperative outcomes after the loss of the exocrine and endocrine functions of the pancreas^[1,3].

Murphy *et al.*^[5] reported that there was an increase in the rate of TP in the United States between 1998 and 2006. In about a 20-year span, 50.5% of the TP on this series were performed during the last 6 years of the study. In this publication, there was increased utilization of elective TP, especially after early diagnosis of multifocal pancreatic pathologies like IPMN and multiple PNET, and the role of TP in the management of chronic pancreatitis was limited only to patients with refractory pain not responding to medical treatment.

On the other hand, there was significant decline in the use of emergency TP as in POPF and hemorrhage. This was mainly due to better use of radiologic drainage and arterial embolization which became available and preferable to relaparotomy^[6]. In our study, we had only 1 patient who underwent an emergency TP for abdominal trauma.

The recommendations of the international consensus guidelines in the management of IPMN depended on its site in the main duct or side branches and its clinical and morphological picture in preoperative imaging study. TP should be performed in patients with positive multiple surgical margins for invasive IPMN or high-grade dysplasia on frozen section^[13]. In our study, the existence of main duct IPMN as the primary pathology accounted for 38.8% of all TP performed, and IPMN associated with other tumors accounted for 21.4%, but elsewhere IPMN has been reported to encompass 22% of all TP performed^[3].

Dallemagne *et al.*^[18] demonstrated the feasibility

Table 3 Postoperative outcomes and complications (90 d) for 103 patients undergoing total pancreatectomy

Variable	Overall (n = 103)	PDAC (n = 42)	IPMN (n = 40)	LTP (n = 24)
Cardiac	10 (9.7%)	5 (11.9%)	3 (7.5%)	1 (4.2%)
Pulmonary	15 (14.6%)	7 (16.7%)	6 (15%)	5 (20.8%)
Renal insufficiency	8 (7.8%)	3 (7.1%)	6 (15%)	4 (16.7%)
Hepatic insufficiency	3 (2.4%)	1 (2.4%)	3 (7.5%)	2 (8.3%)
Major glycemic event	6 (5.8%)	3 (7.1%)	2 (5%)	1 (4.2%)
Post-pancreatectomy hemorrhage	5 (4.9%)	0 (0.0%)	4 (10%)	4 (16.7%)
A	2 (1.9%)	0	2 (5%)	2 (8.3%)
B	1 (0.8%)	0	0	1 (4.2%)
C	2 (1.9%)	0	2 (5%)	1 (4.2%)
Delayed gastric emptying	14 (13.6%)	5 (11.9%)	5 (12.5%)	2 (8.3%)
A	4 (4.9%)	2 (4.8%)	2 (5%)	0
B	5 (4.9%)	2 (4.8%)	1 (2.5%)	1 (4.2%)
C	5 (4.9%)	1 (2.4%)	2 (5%)	1 (4.2%)
Wound infection	11 (10.7%)	5 (11.9%)	2 (5%)	2 (8.3%)
Intra-abdominal abscess	14 (13.6%)	2 (4.8%)	8 (20%)	4 (16.7%)
Biliary fistula	2 (1.9%)	0	1 (2.5%)	0
Mesenteric/portal vein thrombosis	5 (4.9%)	2 (4.8%)	2 (5%)	1 (4.2%)
Reoperation	7 (6.8%)	2 (4.8%)	2 (5%)	2 (8.3%)
Patients intensive care stay	64 (62.1%)	24 (57.1%)	30 (75%)	10 (41.7%)
Median intensive care stay, d ¹ (range)	2 (1-59)	2 (1-12)	2 (1-59)	2 (1-33)
Overall morbidity	66 (64.1%)	27 (64.3%)	25 (62.5%)	10 (41.7%)
Major (III - V)	33 (32%)	13 (31%)	13 (32.5%)	5 (20.8%)
IIIa	14 (13.6%)	5 (11.9%)	6 (15%)	0
IIIb	3 (2.9%)	2 (4.8%)	0	0
IVa	4 (4.9%)	1 (2.4%)	2 (5%)	2 (8.3%)
IVb	5 (4.9%)	2 (4.8%)	1 (2.5%)	2 (8.3%)
V	7 (6.8%)	3 (7.1%)	4 (10%)	1 (4.2%)
Length of stay, d ¹ (range)	9 (3%-71%)	9 (3%-71%)	10 (4%-67%)	8 (4%-52%)
Readmission	26 (25.2%)	12 (28.6%)	8 (20%)	3 (12.5%)

¹Values are median (range), values in parenthesis are percentages unless otherwise indicated. IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy; PDAC: Pancreatic ductal adenocarcinoma.

and advantage of TP with the laparoscopic approach. They reported two cases of TP with pylorus and splenic preservation with good postoperative outcomes. Blood loss, intensive care unit length of stay, and overall hospital length of stay were shorter^[19-21]. Asbun and Stauffer also reported 11 patients with LTP^[19].

Zeh *et al.*^[22] and Buchs *et al.*^[23] reported that robotic assistance LTP can offer more advantages. Giulianotti documented five cases with laparoscopic robotic surgery, with spleen-preserving technique in two of them (Kimura technique)^[24]. Also, Boggi *et al.*^[25] showed the feasibility of robot-assisted LTP in a series of 11 patients without conversion to open surgery.

Choi *et al.*^[26] and Ferrone *et al.*^[27] reported four patients with laparoscopic-assisted pylorus and spleen-preserving TP with segmental excision of the splenic artery and vein (Warshaw's procedure), but with a small midline opening for completion of the anastomosis.

In our study, 24 patients underwent full LTP, 16 underwent pylorus-preserving LTP, and 5 underwent spleen-preserving LTP. Patients with LTP had a higher negative margins rate and significantly more lymph nodes removed than in open surgery.

There are still high postoperative complications after TP. In our study, 32% of patients had a major complication after TP. This matches with other series that had complication rates of 32%-54%^[4,28]. However,

the complications after partial resection and TP were not significantly different in one study done on 124 patients with TP^[29].

The postoperative outcomes related to exocrine and endocrine pancreatic functions may affect the enthusiasm for TP. Postoperative diabetes may be difficult to control, with reported mortality from hypoglycemia^[30,31]. In our study, no such deaths were reported. The improvements in insulin, well-trained nurses, and exposure to a diabetic care team prior to the procedure led to dramatically improved diabetic outcomes post-TP^[30,32]. Since 2008, at our institution, we have implemented a preoperative TP pathway in which patients receive glucose management, enzyme replacement, and nutritional education prior to the operation. The indications and management decisions are done through discussion at a multidisciplinary Pancreas Board that is held on a weekly basis.

Wu *et al.*^[33] reported that islet autotransplantation (IAT) is a safe modality for patients who had chronic pancreatitis and underwent TP, and a significant number of patients can achieve insulin independence for a long time after receiving enough islet equivalent per kg body weight. None of our patients who underwent TP for chronic pancreatitis were candidates for TP and IAT as all had concerns for neoplasia. Any candidate for TP and IAT are sent to those referral centers. Hence, there is a possible bias towards a small number of patients

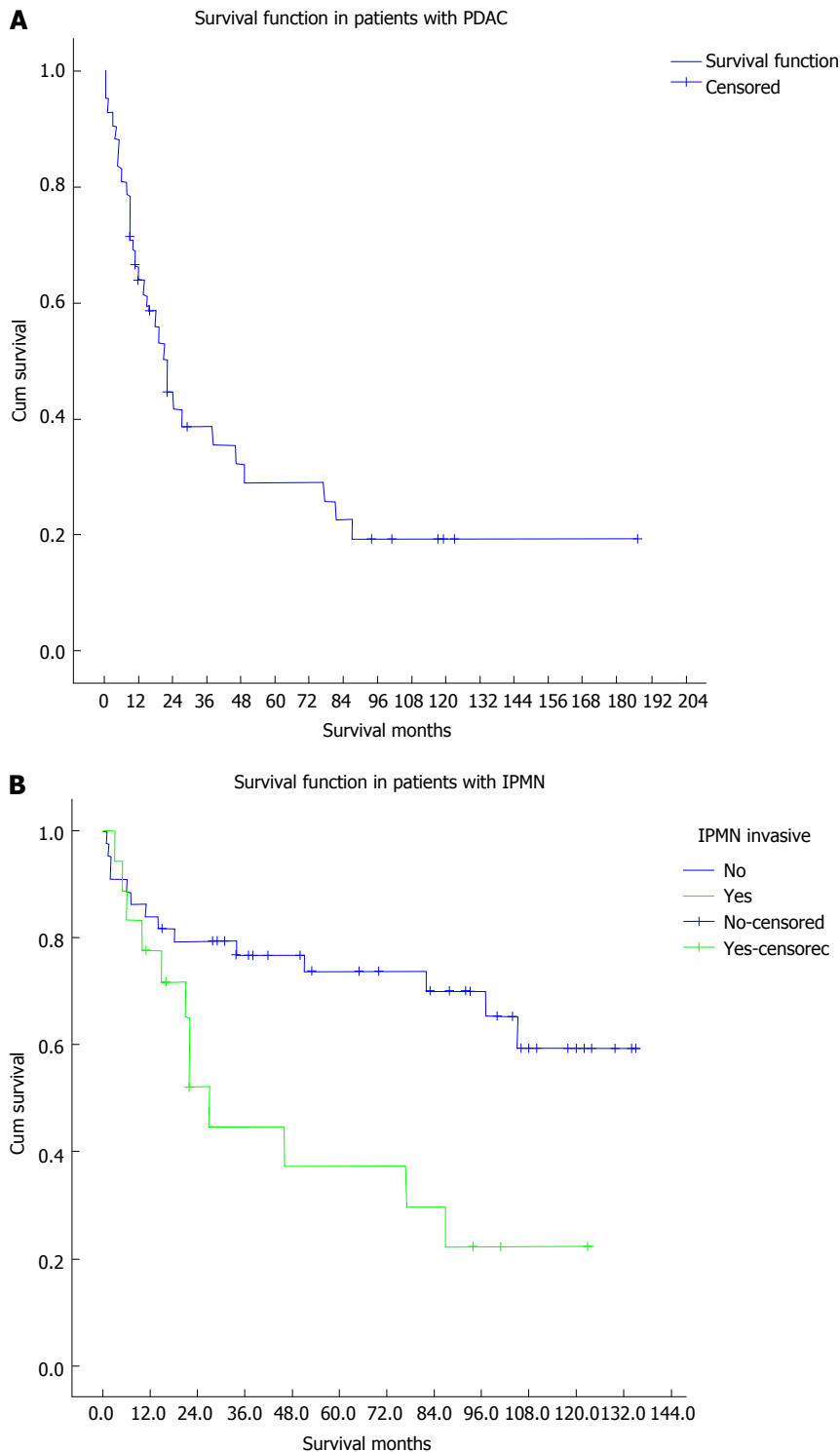


Figure 1 Kaplan Meier curve for survival. A: Survival in patients with pancreatic ductal adenocarcinoma; B: Survival in patients with intraductal papillary mucinous neoplasms. PDAC: Pancreatic ductal adenocarcinoma; IPMN: Intraductal papillary mucinous neoplasms.

undergoing TP for chronic pancreatitis at our institution.

The development of enzyme replacement formulations and the use of the duodenum-preserving TP have improved morbidity from exocrine insufficiency. However, in one study, the pylorus-preserving TP was not associated with significantly different nutritional status than the standard TP^[34].

Intraoperative frozen section analysis of the resection

margins during partial pancreatectomies is important to emphasize R0 resection. There was a significantly better survival in patients undergoing completion TP after positive margins during PD than patients undergoing R1 resection in a study done on 33 patients with PDAC^[35]. In our study, 21.4% of the patients who underwent distal pancreatectomies and pancreaticoduodenectomies also had positive resection margins in the pathological study

Table 4 Pathologic findings for 103 patients undergoing total pancreatectomy

Variable	Overall (n = 103)	LTP (n = 24)
Malignant	n = 53	n = 12
Pancreatic ductal adenocarcinoma	42 (40.8%)	5 (20.8%)
<i>De novo</i>	23 (22.3%)	3 (12.5%)
Arising from IPMN	19 (18.5%)	2 (8.3%)
Neuroendocrine	7 (6.8%)	6 (25%)
Cholangiocarcinoma with IPMN	1 (0.97%)	0
Ampullary adenocarcinoma with IPMN	1 (0.97%)	1 (4.2%)
Renal cell carcinoma	1 (0.97%)	0
Sarcoma	1 (0.97%)	0
Tumor size, cm ¹	3.5 ± 2.4 (0.5%-14%)	3.2 ± 2.5 (1.3%-10%)
Margin negative (R0)	41 (77.4%)	11 (91.7%)
Number of lymph nodes harvested ¹	23 ± 14 (1%-61%)	28 ± 11 (11%-41%)
Non malignant	n = 50	n = 12
IPMN	40 (38.8%)	11 (45.8%)
Chronic pancreatitis	8 (7.8%)	1 (4.2%)
Ampullary adenoma with IPMN	1 (0.97%)	0
Trauma	1 (0.97%)	0

¹Values are mean (range), values in parenthesis are percentages unless otherwise indicated. IPMN: Intraductal papillary mucinous neoplasm; LTP: Laparoscopic total pancreatectomy.

and required TP in the same operative sitting.

Survival of patients undergoing TP varied according to the underlying disease process. Patients with benign disease had a high survival rate whereas those with invasive IPMN or other malignant tumors had poor survival as shown in our study. Some institutions reported high operative mortality rates to be greater than 20% and associated with high morbidity, and this led these centers to stand against the role of TP^[36-38]. However, recent institution series have reported lower perioperative mortality rates to be 3%-6.1%^[4,5,32], which was near to our 90-d perioperative mortality rate of 6.8%. The improved results in recent years are likely due to improvements in perioperative support, education, and possibly, enhanced surgical technique.

In a recent study, Johnston *et al.*^[7] reported that the first month perioperative mortality after TP was 5.5%. The median survival was 15 ms, and the 1-, 3-, and 5-year overall survival rates were 60%, 22% and 13%, respectively. In multivariate analysis, the factors that affected survival were age, positive lymph nodes, positive surgical margin, tumor grade, tumor size, and adjuvant chemotherapy.

Baiocchi *et al.*^[2] and Salvia *et al.*^[39] reported that IPMN was resectable in 90%-100% of the patients. The survival rates for CIS, invasive carcinoma, and presence of nodal metastasis were 80%-90%, 50%-70% and 40%-50%, respectively.

The role of emergency TP is declining in favor of alternative interventional radiological strategies for the management of POPF and hemorrhage. Venous reconstruction in appropriately selected patients with PDAC and locally advanced tumor can be done safely

without negatively affecting recurrence or survival when compared to patients without vein involvement by the tumor. LTP appears to be a feasible and safe procedure when performed by experienced hands at a high-volume center. The significant metabolic derangements after TP may not become immediately apparent in the post-operative inpatient recovery phase, and may lead to a high rate of readmissions later on, so strict follow-up protocol should be available for these patients. A multidisciplinary approach with all-encompassing peri-operative education that includes diabetic and nutritional counseling appears to be essential in the successful management of these patients.

ACKNOWLEDGMENTS

The authors would like to acknowledge the assistance provided by Mauricia Buchanan in data collection.

COMMENTS

Background

In selected patients, total pancreatectomy (TP) has been established as a potential option in the treatment of pancreatic ductal adenocarcinoma, invasive or diffuse intraductal papillary mucinous neoplasms, multiple pancreatic neuroendocrine tumors.

Research frontiers

A single institutional retrospective study of patients undergoing total pancreatectomy from 1995 to 2014 was performed.

Innovations and breakthroughs

TP is performed at an increasing rate at major pancreatic centers, there is still debate regarding its indications and outcomes. This study aimed to analyze the indications and short- and long-term outcomes of TP in the spectrum of pancreatic resections in this high-volume center.

Applications

Total pancreatectomy, including laparoscopic total pancreatectomy, appears to be an appropriate option for selected patients when treated at a high-volume pancreatic center and through a multispecialty approach.

Terminology

The authors conducted a retrospective study of 103 patients who underwent TP between March 1995 and December 2014 at Mayo Clinic in Jacksonville, Florida using data collected from an institutional review board-approved prospective database.

Peer-review

The staff and surgeons are very experienced, presenting excellent post-operative outcome and long-term survival.

REFERENCES

- Kulu Y, Schmied BM, Werner J, Muselli P, Büchler MW, Schmidt J. Total pancreatectomy for pancreatic cancer: indications and operative technique. *HPB* (Oxford) 2009; **11**: 469-475 [PMID: 19816610 DOI: 10.1111/j.1477-2574.2009.00085.x]
- Baiocchi GL, Portolani N, Missale G, Baronchelli C, Gheza F, Cantù M, Grazioli L, Giulini SM. Intraductal papillary mucinous neoplasm of the pancreas (IPMN): clinico-pathological correlations and surgical indications. *World J Surg Oncol* 2010; **8**: 25 [PMID: 20374620 DOI: 10.1186/1477-7819-8-25]

- 3 **Almond M**, Roberts KJ, Hodson J, Sutcliffe R, Marudanayagam R, Isaac J, Muiesan P, Mirza D. Changing indications for a total pancreatectomy: perspectives over a quarter of a century. *HPB* (Oxford) 2015; **17**: 416-421 [PMID: 25406456 DOI: 10.1111/hpb.12365]
- 4 **Stauffer JA**, Nguyen JH, Heckman MG, Grewal MS, Dougherty M, Gill KR, Jamil LH, Scimeca D, Raimondo M, Smith CD, Martin JK, Asbun HJ. Patient outcomes after total pancreatectomy: a single centre contemporary experience. *HPB* (Oxford) 2009; **11**: 483-492 [PMID: 19816612 DOI: 10.1111/j.1477-2574.2009.00077.x]
- 5 **Murphy MM**, Knaus WJ, Ng SC, Hill JS, McPhee JT, Shah SA, Tseng JF. Total pancreatectomy: a national study. *HPB* (Oxford) 2009; **11**: 476-482 [PMID: 19816611 DOI: 10.1111/j.1477-2574.2009.00076.x]
- 6 **Haddad LB**, Scatton O, Randone B, Andraus W, Massault PP, Dousset B, Soubrane O. Pancreatic fistula after pancreaticoduodenectomy: the conservative treatment of choice. *HPB* (Oxford) 2009; **11**: 203-209 [PMID: 19590648 DOI: 10.1111/j.1477-2574.2009.00007.x]
- 7 **Johnston WC**, Hoen HM, Cassera MA, Newell PH, Hammill CW, Hansen PD, Wolf RF. Total pancreatectomy for pancreatic ductal adenocarcinoma: review of the National Cancer Data Base. *HPB* (Oxford) 2016; **18**: 21-28 [PMID: 26776847 DOI: 10.1016/j.hpb.2015.07.009]
- 8 **Jethwa P**, Sodergren M, Lala A, Webber J, Buckels JA, Bramhall SR, Mirza DF. Diabetic control after total pancreatectomy. *Dig Liver Dis* 2006; **38**: 415-419 [PMID: 16527551 DOI: 10.1016/j.dld.2006.01.022]
- 9 **Johnston PC**, Lin YK, Walsh RM, Bottino R, Stevens TK, Trucco M, Bena J, Faiman C, Hatipoglu BA. Factors associated with islet yield and insulin independence after total pancreatectomy and islet cell autotransplantation in patients with chronic pancreatitis utilizing off-site islet isolation: Cleveland Clinic experience. *J Clin Endocrinol Metab* 2015; **100**: 1765-1770 [PMID: 25781357 DOI: 10.1210/jc.2014-4298]
- 10 **Haynes SR**, Lawler PG. An assessment of the consistency of ASA physical status classification allocation. *Anaesthesia* 1995; **50**: 195-199 [PMID: 7717481 DOI: 10.1111/j.1365-2044.1995.tb04554.x]
- 11 **Oken MM**, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-655 [PMID: 7165009 DOI: 10.1097/00000421-198212000-00014]
- 12 **Tanaka M**, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatol* 2006; **6**: 17-32 [PMID: 16327281 DOI: 10.1159/000090023]
- 13 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatol* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]
- 14 **Bockhorn M**, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Büchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhut A, Friess H, Gouma DJ, Hartwig W, Lillemoe KD, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; **155**: 977-988 [PMID: 24856119 DOI: 10.1016/j.surg.2014.02.001]
- 15 **DeOliveira ML**, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, Clavien PA. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. *Ann Surg* 2006; **244**: 931-937; discussion 931-937 [PMID: 17122618 DOI: 10.1097/01.sla.0000246856.03918.9a]
- 16 **Wente MN**, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761-768 [PMID: 17981197 DOI: 10.1016/j.surg.2007.05.005]
- 17 **Wente MN**, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; **142**: 20-25 [PMID: 17629996 DOI: 10.1016/j.surg.2007.02.001]
- 18 **Dallemagne B**, de Oliveira AT, Lacerda CF, D'Agostino J, Mercoli H, Marescaux J. Full laparoscopic total pancreatectomy with and without spleen and pylorus preservation: a feasibility report. *J Hepatobiliary Pancreat Sci* 2013; **20**: 647-653 [PMID: 23430055 DOI: 10.1007/s00534-013-0593-3]
- 19 **Asbun HJ**, Stauffer JA. Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. *J Am Coll Surg* 2012; **215**: 810-819 [PMID: 22999327 DOI: 10.1016/j.jamcollsurg.2012.08.006]
- 20 **Kim SC**, Song KB, Jung YS, Kim YH, Park do H, Lee SS, Seo DW, Lee SK, Kim MH, Park KM, Lee YJ. Short-term clinical outcomes for 100 consecutive cases of laparoscopic pylorus-preserving pancreaticoduodenectomy: improvement with surgical experience. *Surg Endosc* 2013; **27**: 95-103 [PMID: 22752284 DOI: 10.1007/s00464-012-2427-9]
- 21 **Casadei R**, Marchegiani G, Laterza M, Ricci C, Marrano N, Margiotta A, Minni F. Total pancreatectomy: doing it with a mini-invasive approach. *JOP* 2009; **10**: 328-331 [PMID: 19454829]
- 22 **Zeh HJ**, Zureikat AH, Secrest A, Dauoudi M, Bartlett D, Moser AJ. Outcomes after robot-assisted pancreaticoduodenectomy for periampullary lesions. *Ann Surg Oncol* 2012; **19**: 864-870 [PMID: 21947670 DOI: 10.1245/s10434-011-2045-0]
- 23 **Buchs NC**, Addeo P, Bianco FM, Ayloo S, Benedetti E, Giulianotti PC. Robotic versus open pancreaticoduodenectomy: a comparative study at a single institution. *World J Surg* 2011; **35**: 2739-2746 [PMID: 21947494 DOI: 10.1007/s00268-011-1276-3]
- 24 **Giulianotti PC**, Addeo P, Buchs NC, Bianco FM, Ayloo SM. Early experience with robotic total pancreatectomy. *Pancreas* 2011; **40**: 311-313 [PMID: 21311310 DOI: 10.1097/MPA.0b013e3181f7e303]
- 25 **Boggi U**, Palladino S, Massimetti G, Vistoli F, Caniglia F, De Lio N, Perrone V, Barbarello L, Belluomini M, Signori S, Amorese G, Mosca F. Laparoscopic robot-assisted versus open total pancreatectomy: a case-matched study. *Surg Endosc* 2015; **29**: 1425-1432 [PMID: 25159652 DOI: 10.1007/s00464-014-3819-9]
- 26 **Choi SH**, Hwang HK, Kang CM, Yoon CI, Lee WJ. Pylorus- and spleen-preserving total pancreaticoduodenectomy with resection of both whole splenic vessels: feasibility and laparoscopic application to intraductal papillary mucin-producing tumors of the pancreas. *Surg Endosc* 2012; **26**: 2072-2077 [PMID: 22237756 DOI: 10.1007/s00464-011-2113-3]
- 27 **Ferrone CR**, Konstantinidis IT, Sahani DV, Wargo JA, Fernandez-del Castillo C, Warshaw AL. Twenty-three years of the Warshaw operation for distal pancreatectomy with preservation of the spleen. *Ann Surg* 2011; **253**: 1136-1139 [PMID: 21394008 DOI: 10.1097/SLA.0b013e318212c1e2]
- 28 **Crippa S**, Tamburrino D, Partelli S, Salvia R, Germani S, Bassi C, Pederzoli P, Falconi M. Total pancreatectomy: indications, different timing, and perioperative and long-term outcomes. *Surgery* 2011; **149**: 79-86 [PMID: 20494386 DOI: 10.1016/j.surg.2010.04.007]
- 29 **Müller MW**, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, Breisch-Girbig D, Ceyhan GO, Büchler MW. Is there still a role for total pancreatectomy? *Ann Surg* 2007; **246**: 966-974; discussion 974-975 [PMID: 18043098 DOI: 10.1097/SLA.0b013e31815c2ca3]
- 30 **Barbier L**, Jamal W, Dokmak S, Aussilhou B, Corcos O, Ruszniewski P, Belghiti J, Sauvanet A. Impact of total pancreatectomy: short- and long-term assessment. *HPB* (Oxford) 2013; **15**: 882-892 [PMID: 23458647 DOI: 10.1111/hpb.12054]
- 31 **Roberts KJ**, Blanco G, Webber J, Marudanayagam R, Sutcliffe

- RP, Muiesan P, Bramhall SR, Isaac J, Mirza DF. How severe is diabetes after total pancreatectomy? A case-matched analysis. *HPB* (Oxford) 2014; **16**: 814-821 [PMID: 24344937 DOI: 10.1111/hpb.12203]
- 32 **Billings BJ**, Christein JD, Harmsen WS, Harrington JR, Chari ST, Que FG, Farnell MB, Nagorney DM, Sarr MG. Quality-of-life after total pancreatectomy: is it really that bad on long-term follow-up? *J Gastrointest Surg* 2005; **9**: 1059-1066; discussion 1066-1067 [PMID: 16269376 DOI: 10.1016/j.gassur.2005.05.014]
- 33 **Wu Q**, Zhang M, Qin Y, Jiang R, Chen H, Xu X, Yang T, Jiang K, Miao Y. Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients. *Endocr J* 2015; **62**: 227-234 [PMID: 25735805 DOI: 10.1507/endocrj.EJ14-0510]
- 34 **Sugiyama M**, Atomi Y. Pylorus-preserving total pancreatectomy for pancreatic cancer. *World J Surg* 2000; **24**: 66-70; discussion 70-71 [PMID: 10594206]
- 35 **Schmidt CM**, Glant J, Winter JM, Kennard J, Dixon J, Zhao Q, Howard TJ, Madura JA, Nakeeb A, Pitt HA, Cameron JL, Yeo CJ, Lillemoe KD. Total pancreatectomy (R0 resection) improves survival over subtotal pancreatectomy in isolated neck margin positive pancreatic adenocarcinoma. *Surgery* 2007; **142**: 572-578; discussion 572-578 [PMID: 17950350 DOI: 10.1016/j.surg.2007.07.016]
- 36 **Cooperman AM**, Herter FP, Marboe CA, Helmreich ZV, Perzin KH. Pancreatoduodenal resection and total pnacreatectomy--an institutional review. *Surgery* 1981; **90**: 707-712 [PMID: 7281009]
- 37 **Ihse I**, Anderson H. Total pancreatectomy for cancer of the pancreas: is it appropriate? *World J Surg* 1996; **20**: 288-293; discussion 294 [PMID: 8661833]
- 38 **Brooks JR**. Where are we with pancreas transplantation? *Surgery* 1989; **106**: 935-945 [PMID: 2686060]
- 39 **Salvia R**, Fernández-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, Pederzoli P, Warshaw AL. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg* 2004; **239**: 678-685; discussion 685-687 [PMID: 15082972]

P- Reviewer: Sandblom G, Shelat VG **S- Editor:** Qiu S
L- Editor: A **E- Editor:** Li D



Retrospective Study

Short-term and middle-term evaluation of laparoscopic hepatectomies compared with open hepatectomies: A propensity score matching analysis

Xavier Untereiner, Audrey Cagnet, Riccardo Memeo, Vito De Blasi, Stylianos Tzedakis, Tullio Piardi, Francois Severac, Didier Mutter, Reza Kianmanesh, Jacques Marescaux, Daniele Sommacale, Patrick Pessaux

Xavier Untereiner, Riccardo Memeo, Vito De Blasi, Stylianos Tzedakis, Francois Severac, Didier Mutter, Jacques Marescaux, Patrick Pessaux, Department of Digestive Surgery, University Hospital of Strasbourg, 67091 Strasbourg, France

Xavier Untereiner, Riccardo Memeo, Vito De Blasi, Stylianos Tzedakis, Francois Severac, Didier Mutter, Jacques Marescaux, Patrick Pessaux, IHU-Strasbourg, Institute for Image-Guided Surgery, 67091 Strasbourg, France

Xavier Untereiner, Riccardo Memeo, Vito De Blasi, Stylianos Tzedakis, Francois Severac, Didier Mutter, Jacques Marescaux, Patrick Pessaux, INSERM, UMR 1110, 67091 Strasbourg, France

Audrey Cagnet, Tullio Piardi, Reza Kianmanesh, Daniele Sommacale, Department of General, Digestive and Endocrine Surgery, Hôpital Robert Debré, Centre Hospitalier Universitaire de Reims, Université de Reims Champagne-Ardenne, 51100 Reims, France

Author contributions: Untereiner X, Cagnet A, De Blasi V and Piardi T were responsible for data collection and study design; Severac F performed the statistical analysis; Untereiner X and Memeo R prepared the manuscript; Memeo R conceptualized the study; Tzedakis S, Mutter D, Marescaux J, Kianmanesh R, Sommacale D and Pessaux P performed data interpretation and critical review of the manuscript; all co-authors approved the final manuscript.

Institutional review board statement: It's a retrospective study. It's not necessary to have the agreement of the Ethics committee.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Patrick Pessaux, Professor, Head of the Hepatobiliary and Pancreatic Surgical Unit Nouvel Hôpital Civil (NHC) 1, Department of Digestive Surgery, University Hospital of Strasbourg, place de l'hôpital, 67091 Strasbourg, France. patrick.pessaux@chru-strasbourg.fr
Telephone: +33-3-69551563
Fax: +33-3-69551521

Received: January 13, 2016
Peer-review started: January 16, 2016
First decision: January 30, 2016
Revised: June 1, 2016
Accepted: July 11, 2016
Article in press: July 13, 2016
Published online: September 27, 2016

Abstract

AIM

To compare short-term results between laparoscopic hepatectomy and open hepatectomy using a propensity score matching.

METHODS

A patient in the laparoscopic liver resection (LLR) group

was randomly matched with another patient in the open liver resection (OLR) group using a 1:1 allocated ratio with the nearest estimated propensity score. Patients of the LLR group without matches were excluded. Matching criteria included age, gender, body mass index, American Society of Anesthesiologists score, potential comorbidities, hepatopathies, size and number of nodules, preoperative chemotherapy, minor or major liver resections. Intraoperative and postoperative data were compared in both groups.

RESULTS

From January 2012 to January 2015, a total of 241 hepatectomies were consecutively performed, of which 169 in the OLR group (70.1%) and 72 in the LLR group (29.9%). The conversion rate was 9.7% ($n = 7$). The mortality rate was 4.2% in the OLR group and 0% in the LLR group. Prior to and after propensity score matching, there was a statistically significant difference favorable to the LLR group regarding shorter operative times (185 min *vs* 247.5 min; $P = 0.002$), less blood loss (100 mL *vs* 300 mL; $P = 0.002$), a shorter hospital stay (7 d *vs* 9 d; $P = 0.004$), and a significantly lower rate of medical complications (4.3% *vs* 26.4%; $P < 0.001$).

CONCLUSION

Laparoscopic liver resections seem to yield better short-term and mid-term results as compared to open hepatectomies and could well be considered a privileged approach and become the gold standard in carefully selected patients.

Key words: Laparoscopic hepatectomy; Morbidity and mortality; Hepatocellular carcinoma; Liver resection; Colorectal metastases; Open hepatectomy; Propensity score matching

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This is a retrospective study to compare short-term results between laparoscopic hepatectomy and open hepatectomy using a propensity score matching. Each patient in the laparoscopic liver resection group was randomly matched with another patient in the open liver resection group using a 1:1 allocated ratio with the nearest estimated propensity score. Prior to and after propensity score matching, results were in favour of laparoscopic liver resection. Laparoscopic liver resections seem to yield better short-term and mid-term results as compared to open approach and could well be considered a privileged approach and become the gold standard in carefully selected patients.

Untereiner X, Cagnet A, Memeo R, De Blasi V, Tzedakis S, Piardi T, Severac F, Mutter D, Kianmanesh R, Marescaux J, Sommacale D, Pessaux P. Short-term and middle-term evaluation of laparoscopic hepatectomies compared with open hepatectomies: A propensity score matching analysis. *World J Gastrointest Surg*

2016; 8(9): 643-650 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/643.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.643>

INTRODUCTION

Since the development of laparoscopic cholecystectomy in 1987, the laparoscopic approach extended to several abdominal procedures. However, it took a very long time for laparoscopic liver surgery to expand.

The first non-anatomical liver resection was described by Reich *et al*^[1] in 1991 and the first anatomical hepatectomy was described by Azagra *et al*^[2] in 1996. Historically, laparoscopy was used to evaluate hepatic lesions before an open hepatectomy^[3,4] or to evaluate the carcinomatosis or peritoneal spread before the surgery and to treat cystic lesions by means of fenestrations^[5,6]. Surgical techniques were progressively developed to propose resections of benign^[2], then malignant lesions (hepatocellular carcinomas and hepatic metastases)^[7,8].

The main reasons accountable for this lack of enthusiasm for laparoscopic hepatectomies, in addition to the technical complexity of interventions, were the lack of appropriate instrumentation, the risk of gas embolism, the risks of uncontrolled bleeding, the fear of not being able to follow oncological principles with a subsequent risk of tumoral dissemination. However, some surgical teams decided to look into the possibilities of laparoscopic hepatic resections.

Indications for laparoscopic hepatectomies were defined during the first international consensus conference held in Louisville, United States^[9] in 2008 and revised in Morioka^[10] in 2014. This approach was used for patients selected with the following criteria: Location and size of lesions, liver function, and the experience of the surgical team. Although it was demonstrated that the laparoscopic approach elicits several advantages in the short- and mid-term (less postoperative pain, quicker restoration of bowel habits, less respiratory and parietal morbidity, improved quality of life, and reduced hospital stay)^[11,12], laparoscopic liver surgery remains currently limited to simple and peripheral resections, and few extensive and complex resections were reported^[13].

In the literature, such series include few patients and most monocentric series are retrospective ones with potential selection biases.

The objective of our study was to evaluate the short-term and mid-term results of laparoscopic hepatectomies as compared to open hepatectomies using a propensity score matching in order to rule out selection biases.

MATERIALS AND METHODS

From January 2012 to January 2015, data of all patients who consecutively underwent hepatectomy in two University hospital settings were collected prospectively.

All patients who required liver surgery whatever the pathology (metastasis, hepatocellular carcinoma, adenoma, neuroendocrine tumor, cholangiocarcinoma, *etc.*) were included. The laparoscopic approach did not modify the operative indications established for open surgery. Indications for laparoscopic hepatectomies were determined according to the latest recommendations^[9,10]. Exclusion criteria for the laparoscopic approach included the following: A poorly defined lesion or a lesion proximal to main vessels, decompensated cirrhosis or severe heart or respiratory failure^[14]. The following variables were analyzed: Type of liver resections (segmentectomies, bisegmentectomies, wedge resections, *etc.*), use of radiofrequency, number of resected segments, operative time, number of clampings, duration and type of clamping, rate of conversion, blood loss, number of transfusions, length of hospital stay, rate of R0 resection margins. All postoperative complications were indexed, namely respiratory (atelectasis, pneumopathy), cardiovascular (cardiac rhythm disorders, ischemia, cardiac decompression, hypertension), renal (acute renal failure, pyelonephritis, cystitis), parietal infections, deep collections, bleeding, biliary fistulas, liver failure, ascites. Liver segmentation was defined according to the Couinaud classification^[15]. Liver resections were defined according to the Brisbane classification in 2000^[16], using the following definitions: Hepatectomy was defined as major when 3 or more segments were removed. Other hepatectomies, which were limited, were performed on 2 segments or less (standard segmentectomy, bisegmentectomy or subsegmentectomy). Postoperative mortality and morbidity was defined as death or complications which occurred in the first 90 postoperative days and were graded according to the Clavien-Dindo classification^[17,18].

Complications were indexed as medical complications, including respiratory complications (atelectasis, pneumopathy), cardiovascular complications (including cardiac rhythm disorders, ischemia, cardiac decompression, hypertension), renal complications (acute renal failure, pyelonephritis, cystitis liver failure, ascites, and as surgical complications including parietal infections, deep collections, biliary fistulas, bleeding, eviscerations, parietal collections and acute digestive ischemia).

Preoperative evaluation

A complete patient evaluation included computed tomography-scan and/or magnetic resonance imaging acquired in 3 phases with a volumetric rendering. Patient personal files were discussed in a multidisciplinary meeting. Resectability was defined by the absence of extrahepatic invasion, the absence of ascites, and a normal liver function. All hepatic resections were performed by expert surgeons skilled in both laparoscopic and open hepatobiliary surgery.

Propensity score matching

All demographic and preoperative data of patients operated on using the open liver resection (OLR) group or the laparoscopic liver resection (LLR) group were compared using a univariate analysis in order to evaluate

the comparability of both groups. A propensity score matching was calculated to take into account and limit selection biases as well as confusion between the two groups. This method allows comparing the effects of the two types of intervention (open vs laparoscopy) taking into account the variables which influence the choice of the procedure type. The propensity score was assessed using logistic regression including the following variables: Age, gender, co-morbidity, American Society of Anesthesiologists (ASA) score, the use of neoadjuvant therapy, body mass index, total number of nodules, and type of resection. The choice of such variables was based on the results of the univariate analysis and/or the known influence of specific factors on the selection of the intervention type. A 1:1 balance ratio was used for propensity score matching, based on the nearest matching PS method^[19-21]. After the matching process, both groups were compared regarding their initial characteristics in order to re-evaluate the comparability of both groups. Finally, matched groups could be compared regarding the different variables of interest in the study.

Statistical analysis

Asymmetrical quantitative variables were presented as medians combined with the first and third quartiles after their distribution had been evaluated. Qualitative variables were presented as numbers and percentages. Comparison of the quantitative variables was performed using a Mann-Whitney test. Comparison of qualitative variables was performed using Pearson's χ^2 test or Fisher's exact test depending on numbers. A *P* value < 0.05 was considered as significant. Analyses were performed using the 3.2.0 version R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population and short-term results prior to matching

Between January 2012 and January 2015, a total of 241 consecutive hepatectomies were performed, including 169 hepatectomies using laparotomy (70.1%) and 72 laparoscopic ones (29.9%), including 8 which were performed by means of the da VinciTM robotic surgical system (*da Vinci SiTM* System; Intuitive Surgical, Inc., Sunnyvale, CA, United States).

As for patient characteristics, both groups were comparable, except for gender ratio (*P* = 0.042), the existence of a co-morbidity (67.5% of patients in the OLR group and 54.2% of patients in the LLR group, *P* = 0.0499), the existence of a hepatopathy including hepatic steatosis and cirrhotic livers (13% in the OLR group vs 36.1% in the LLR group, *P* < 0.001), and preoperative chemotherapy (59.8% in the OLR group vs 36.1% in the LLR group, *P* < 0.001) (Table 1). In addition, there were statistically more lesions in the OLR group as compared to the LLR group 3.0 (1.0-5.0) vs 1.0 (1.0-2.0); *P* < 0.001 and more major hepatectomies in the OLR group as compared to the LLR group (40.8% vs 12.5%, *P* <

Table 1 Demographic data and preoperative variables before and after propensity score matching *n* (%)

	OLR (<i>n</i> = 169)	LLR (<i>n</i> = 72)	<i>P</i> value	OLR (<i>n</i> = 72)	LLR (<i>n</i> = 72)	<i>P</i> value
Gender (M:F)	106:63	35:37	0.042	37:35	35:37	0.739
Age (yr), median (IQR)	65 (58-71)	61 (49-71)	0.091	62 (52-67)	61 (49-71)	0.794
BMI (kg/m ²), median (IQR)						
< 30	141 (83.74)	58 (80.6)	0.590	58 (80.6)	59 (81.9)	0.831
> 30	28 (16.6)	14 (19.4)		14 (19.4)	13 (18.1)	
Co-morbidities	114 (67.5)	39 (54.2)	0.0499	43 (59.7)	39 (54.2)	0.501
Dyslipidemia	53 (31.4)	16 (22.2)	0.151	20 (27.8)	16 (22.2)	0.441
Diabetes	27 (16.0)	12 (16.7)	0.894	10 (13.9)	12 (16.7)	0.643
Hypertension	60 (35.5)	28 (38.9)	0.617	24 (33.3)	28 (38.9)	0.488
Deep venous thrombosis/pulmonary embolism	20 (11.8)	6 (8.3)	0.423	6 (8.3)	6 (8.3)	1
Arteriopathy	8 (4.7)	3 (4.2)	1	1 (1.4)	3 (4.2)	0.620
Renal failure	7 (4.1)	1 (1.4)	0.442	1 (1.4)	1 (1.4)	1
Hepatopathy	22 (13.0)	26 (36.1)	< 0.001	14 (19.4)	26 (36.1)	0.026
Cirrhosis	18 (10.7)	21 (29.2)	0.002	10 (13.9)	21 (29.2)	0.067
Steatosis	11 (6.5)	4 (5.6)		3 (4.2)	4 (5.6)	
Sains	140 (82.8)	47 (65.3)		59 (81.9)	47 (65.3)	
Cardiopathy	35 (20.7)	9 (12.5)	0.131	10 (13.9)	9 (12.5)	0.806
Arrhythmia-atrial fibrillation	9 (5.3)	3 (4.2)	1	2 (2.8)	3 (4.2)	1
COPD	13 (7.7)	11 (15.3)	0.072	2 (2.8)	11 (15.3)	0.02
ASA score (I / II / III) (<i>n</i>)	36/82/51	26/28/18	0.055	21/34/17	26/28/18	0.565
ASA1 + 2	118 (69.8)	54 (75.0)	0.416	55 (76.4)	54 (75.0)	1
ASA3 + 4	51 (30.2)	18 (25.0)	0.416	17 (23.6)	18 (25.0)	1
Preoperative chemotherapy	101 (59.8)	26 (36.1)	< 0.001	30 (41.7)	26 (36.1)	0.494
Number of nodules, median (IQR)	3.0 (1.0-5.0)	1.0 (1.0-1.0)	< 0.001	1.5 (1.0-2.0)	1.0 (1.0-1.0)	< 0.001
Nodule max. size (mm), mean (IQR)	30.0 (20.0-45.0)	26.5 (20.0-44.3)	0.352	26.5 (20.0-44.3)	30.0 (20.0-55.3)	0.138
Resection type						
Major resection	69 (40.8)	9 (12.5)	< 0.001	15 (20.8)	9 (12.5)	0.180
Minor resection	100 (59.2)	63 (87.5)		57 (79.2)	63 (87.5)	
Benign lesions						
Adenoma	3 (1.8)	9 (12.5)	0.001	3 (4.2)	9 (12.5)	0.129
Nodular hyperplasia	2 (1.2)	3 (4.2)	0.159	2 (2.8)	3 (4.2)	1
Hydatid cysts	5 (3.0)	2 (2.8)	1	3 (4.2)	2 (2.8)	1
Angioma	1 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Other pathologies (Caroli disease, sclerosing cholangitis, traumatic, etc.)	2 (1.2)	2 (2.8)	0.585	2 (2.8)	2 (2.8)	1
Malignant tumors						
Hepatocellular carcinoma	25 (14.8)	24 (33.3)	0.001	11 (15.3)	24 (33.3)	0.012
Colorectal metastases	101 (59.8)	18 (25.0)	< 0.001	38 (52.8)	18 (25.0)	< 0.001
Cholangiocarcinoma	11 (6.5)	5 (6.9)	1	4 (5.6)	5 (6.9)	1
Gallbladder cancer	1 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Klatskin tumor	2 (1.2)	1 (1.4)	1	2 (2.8)	1 (1.4)	1
Neuroendocrine tumors	7 (4.1)	1 (1.4)	0.442	5 (6.9)	1 (1.4)	0.209
Other types of metastasis	25 (14.8)	24 (33.3)	0.001	11 (15.3)	24 (33.3)	0.012
Preoperative blood test, median (IQR)						
Albumin (g/dL)	40.0 (38.0-43.0)	41.0 (39.0-44.0)	0.293	40.5 (38.0-44.0)	41.0 (39.0-44.3)	0.465

OLR: Open liver resection; LLR: Laparoscopic liver resection; ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease.

0.001). There was a significant difference concerning pathologies with 9 adenoma resections in the LLR group (12.8%), vs 3 in the OLR group (1.8%) ($P = 0.001$), 24 hepatocarcinomas in the LLR group (33.3%) vs 25 in the OLR group (14.8%), ($P = 0.001$), and 101 colorectal metastasis resections in the OLR group (59.8%) vs 18 in the LLR group (25%), $P < 0.001$ (Table 1).

Details of the procedures performed are outlined in Table 2. It can be observed that fewer segments were resected in the LLR group (median of 1 vs 2; $P < 0.001$) and that there were more segmentectomies performed in the LLR group (40.3% vs 7.1%; $P < 0.001$), fewer bisegmentectomies (13.9% vs 27.2%, $P = 0.025$), fewer right hepatectomies (4.2% vs 15.4%,

$P = 0.014$) and fewer associations with destruction by radiofrequency (12.5% vs 32%, $P = 0.002$) as compared to the OLR group. There was a statistically significant difference in favor of LLR concerning operative time, blood loss, and length of hospital stay. In addition, there were significantly fewer medical complications in the LLR group (4.2% vs 2.8%, $P < 0.001$), taking all types into account (Table 2).

The conversion rate was 9.7% ($n = 7$), the reason for that being the presence of several pedicular adenopathies, which required an extensive dissection in one patient, and there were difficulties of access in 6 other patients. The mortality rate was 4.2% in the OLR group and 0% in the LLR group. The reason for death

Table 2 Operative and postoperative data before and after propensity score matching *n* (%)

	OLR (<i>n</i> = 169)	LLR (<i>n</i> = 72)	<i>P</i> value	OLR (<i>n</i> = 72)	LLR (<i>n</i> = 72)	<i>P</i> value
Resection type						
Bisegmentectomy	46 (27.2)	10 (13.9)	0.025	30 (41.7)	10 (13.9)	< 0.001
Segmentectomy	12 (7.1)	29 (40.3)	< 0.001	8 (11.1)	29 (40.3)	< 0.001
Wedge resection	49 (29.0)	24 (33.3)	0.502	20 (27.8)	24 (33.3)	0.469
Left hepatectomy	23 (13.6)	5 (6.9)	0.188	8 (11.1)	5 (6.9)	0.383
Right hepatectomy	26 (15.4)	3 (4.2)	0.014	6 (8.3)	3 (4.2)	0.494
Enlarged right hepatectomy	15 (8.9)	1 (1.4)	0.044	2 (2.8)	1 (1.4)	1
Combined resection and radiofrequency	54 (32.0)	9 (12.5)	0.002	13 (18.1)	9 (12.5)	0.354
Number of resected segments, median (IQR)	2.0 (0.0-4.0)	1.0 (0.0-1.3)	< 0.001	2.0 (0.0-2.0)	1.0 (0.0-1.3)	0.004
Operation length (min), median (IQR)	250 (190-330)	185 (150-254)	< 0.001	247.5 (187.5-332.5)	185.0 (150.0-253.8)	0.002
Pedicular clamping	110 (65.1)	40 (55.6)	0.162	43 (59.7)	40 (55.6)	0.613
Intermittent	96 (56.8)	34 (47.2)	0.354	36 (50.0)	34 (47.2)	0.739
Permanent	14 (8.3)	6 (8.3)		7 (9.7)	6 (8.3)	0.771
No clamping	59 (34.9)	32 (44.4)		29 (40.3)	32 (44.4)	0.613
Clamping duration (min), median (IQR)	22.0 (0.0-38.0)	15.0 (0.0-35.0)	0.174	25.0 (0.0-36.5)	15.0 (0.0-35.0)	0.411
Blood loss (mL), median (IQR)	300 (30-500)	100 (30-356)	0.003	300.0 (30.0-562.5)	100.0 (30.0-356.3)	0.002
Transfusion (<i>n</i>), median (IQR)	41 (24.3)	12 (16.7)	0.193	16 (22.2)	12 (16.7)	0.400
Length of hospital stay (d), median (IQR)	10.0 (7.0-14.0)	7.0 (5.8-10.0)	< 0.001	9.0 (7.0-12.0)	7.0 (5.8-10.0)	0.004
R0 resection margin	139 (82.3)	63 (87.5)	0.311	62 (86.1)	63 (87.5)	0.806
Conversion rate	NA	7 (9.7)	0.065	NA	7 (9.7)	0.326
Postoperative complications \geq 1						
Respiratory	30 (17.8)	6 (8.3)	0.060	18 (25.0)	6 (8.3)	0.007
Atelectasis	21 (12.4)	4 (5.6)	0.109	11 (15.3)	4 (5.6)	0.056
Pneumopathy	10 (5.9)	2 (2.8)	0.518	7 (9.7)	2 (2.8)	0.166
Renal	7 (4.1)	0 (0.0)	0.107	5 (6.9)	0 (0.0)	0.058
Acute renal failure	6 (3.6)	0 (0.0)	0.183	5 (6.9)	0 (0.0)	0.058
Cystitis/pyelonephritis	1 (0.6)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Cardiovascular	7 (4.1)	4 (5.6)	0.737	2 (2.8)	4 (5.6)	0.681
Wall infection	8 (4.7)	2 (2.8)	0.728	6 (8.3)	2 (2.8)	0.275
Deep collection	19 (11.2)	6 (8.3)	0.498	8 (11.1)	6 (8.3)	0.574
Hemorrhage	3 (1.8)	0 (0.0)	0.556	2 (2.8)	0 (0.0)	0.497
Liver failure	7 (4.1)	1 (1.4)	0.442	4 (5.6)	1 (1.4)	0.366
Ascites	5 (3.0)	2 (2.8)	1	5 (6.9)	2 (2.8)	0.441
Biliary fistula	10 (5.9)	2 (2.8)	0.518	1 (1.4)	2 (2.8)	1
Medical complications	47 (27.8)	3 (4.3)	< 0.001	19 (26.4)	3 (4.3)	< 0.001
Surgical complications	7 (4.1)	2 (2.8)	0.729	4 (5.6)	2 (2.8)	0.681
I - II	47 (27.8)	21 (29.2)	0.690	21 (29.2)	21 (29.2)	0.447
III-IV	33 (19.5)	12 (16.7)		13 (18.1)	12 (16.7)	
V	4 (2.4)	0 (0.0)		3 (4.2)	0 (0.0)	
Postoperative mortality 30 d	2 (1.2)	0 (0.0)	1	2 (1.2)	0 (0.0)	0.080
Postoperative mortality 60 d	3 (1.8)	0 (0.0)	0.556	0 (0.0)	0 (0.0)	1
Postoperative mortality 90 d	5 (3.0)	0 (0.0)	0.326	0 (0.0)	0 (0.0)	1

OLR: Open liver resection; LLR: Laparoscopic liver resection.

was the occurrence of multivisceral failure after a right hepatectomy in 3 ASA 3 patients including 2 who were treated for a cholangiocarcinoma and one for liver metastases of a colorectal cancer which received 3 cycles of neoadjuvant FOLFOX therapy.

Population and short-term results after matching and PS

After using the propensity score, all 72 patients of the LLR group were matched to 72 patients of the OLR group. Both groups were comparable as far as patient characteristics were concerned, except for liver diseases which were more important in the LLR group (36.1% vs 19.4%, $P = 0.026$), the type of segment resected ($P < 0.05$), and

the pathology, with more hepatocellular carcinomas in the LLR group (33.3% vs 15.3%, $P = 0.012$) and fewer colorectal metastases (25% vs 52.8% in the OLR group, $P < 0.001$), (Table 1). More bisegmentectomies were performed in the OLR group (41.7% vs 13.9%, $P < 0.001$) but more segmentectomies in the LLR group (40.3% vs 11.1%, $P < 0.001$).

There was still a significant difference in terms of operative time ($P = 0.002$), a shorter hospital stay ($P = 0.004$) in the LLR group, less blood loss ($P = 0.002$), and fewer medical complications (4.3% vs 26.4%, $P < 0.001$) in the LLR group. Other values from both groups were comparable (Table 2).

DISCUSSION

The objective of this study was to compare short-term results of hepatectomies performed using a laparoscopic and an open approach, using the propensity score in order to reduce the selection bias. After matching, it has more open resection for liver metastases of a colorectal cancer than the laparoscopic approach. Indeed in colorectal cancer, metastases are often multiple and difficult to be able to remove by laparoscopic approach. Among the population, there was a selection of indications with more limited and minor resections in the laparoscopic group with fewer resected lesions. After a matching and a propensity score were applied to the essential factors which influence morbi-mortality, a significant decrease in blood loss could be observed, as well as the length of hospital stay, operative time, and postoperative medical complications in the laparoscopic group.

Despite an increase in the number of centers which use laparoscopic hepatobiliary surgery, the use of this approach is not very widespread (5% to 30% of liver resections)^[22-27]. Only a few centers report a strong activity representing 50% to 80%^[28-30] of liver resections. Over a period of 3 years, we report 72 laparoscopic hepatectomies, out of 241 hepatectomies in total, which means that 29.9% of hepatectomies were performed laparoscopically. Our indications for laparoscopic hepatectomy are the same as for open surgery. Most often, we would decide to choose a laparoscopic approach due to the location and the size of the tumor^[9,10]. As shown in our series, laparoscopic is most often used for anterolateral resections (segments 2 to 6). Wedge resections, segmentectomies, and left lobectomies remain the best laparoscopic indications^[22,30,31]. Major hepatectomies, especially right hepatectomies, were mainly performed using an open approach due to technical difficulties^[32-36]. Resection of lesions located in segments VII, VIII, I va and I is still not properly documented due to exposure difficulties and proximity with the inferior vena cava and suprahepatic veins. Superior posterior segments can be approached using transdiaphragmatic ports^[37,38], or using a transthoracic route^[39]. In addition, laparoscopic resection is not recommended for lesions greater than 5 cm in diameter, due to manipulation difficulties with a risk of tumoral rupture and of obtaining insufficient resection margins^[22,26,29]. The hepatic pedicle is systematically controlled at the beginning of the intervention in order to perform a pedicular clamping if required (55.6% of cases in our series). We report 6 permanent clampings but this corresponds to very superficial resections. In most cases, we privileged intermittent clamping, as this allows for a better liver tolerance, especially in cirrhotic patients^[40-42], as well as a better short- and long-term prognosis^[43]. We used intermittent clamping using a laparoscopic approach systematically. Additionally, laparoscopic clamping, which is associated with pneumoperitoneum pressure, allows to decrease bleeding and almost completely eliminates the use of continuous aspiration, which is not feasible.

Average clamping time was 15 min with the LLR vs 22 min with the OLR ($P = 0.174$). Intermittent clamping was 20 min with reperfusion phases of 10 min in all patients, except for cirrhotic patients, in which clamping would not exceed 15 min.

In addition, we do not report any gas embolism in our series, a rare occurrence which has, however, previously been described in laparoscopic surgery^[22,27,28]. It has been demonstrated that in order to decrease this risk, the use of carbon dioxide (a highly soluble gas) should be privileged, as well as low insufflations pressures^[44]. We did not use Argon although it allows for a good hemostasis, because it increases the risk of gas embolism in liver surgery^[45].

After PS, our study clearly demonstrated the benefits of the laparoscopic approach. There was a decrease in intraoperative bleeding (100 mL vs 300 mL, $P = 0.002$), a reduction in the length of hospital stay^[11] with a median of 7 d vs 9 d ($P = 0.004$) and even a shorter operative time (185 min vs 247.5 min, $P = 0.002$). The same goes for postoperative outcomes which appear to be simpler with fewer medical complications, especially respiratory ones (4.3% vs 26.4%, $P < 0.001$), also described in the series by Fuks *et al.*^[46]. As for surgical complications, laparoscopy does not provide any real benefits. Some authors have reported similar results^[47-49], like Cannon *et al.*^[50] (23% vs 50%, $P = 0.004$), Simillis in his meta-analysis^[51]. In the laparoscopic group, no deaths have been recorded; the same goes for unusual complications, and less than 20% of patients were transfused during hospitalization.

The conversion rate described in the literature ranges from 5% to 15%^[22-24,30]. The 2 main reasons for conversion are: Firstly, a technical problem due to a difficult exposure, a risk of tumoral rupture dissemination for fragile lesions or a doubt concerning the sufficient resection margin. The second reason is uncontrolled bleeding. In our series, we report a conversion rate of 9.7%, the main reason for it being exposure difficulties, which make resection difficult.

The results were obtained in our series as well as in series published by surgeons with experience in liver surgery and laparoscopic surgery, and consequently these results can only be extrapolated with caution in all centers.

In conclusion, the development of liver surgery using a laparoscopic approach has been a gradual process, and some liver resections currently seem feasible and safe in patients selected in centers in which surgeons have experience in both hepatic surgery and laparoscopic surgery. This study compared the complications mainly for minor resections after matching; although bicentric study with small groups, the laparoscopic liver resections seem to produce the same results as the open approach in the short- and middle-term. It could be considered as an alternative to open surgery and become the gold standard for carefully selected patients. However, complementary studies seem necessary, especially for long-term oncological results and for major hepa-

tectomies, in order for the laparoscopic approach to become a widely used alternative to hepatectomies using laparotomy.

COMMENTS

Background

Laparoscopic surgery is a consolidate technique who is diffusing rapidly also in some subspeciality who initially were contraindicated.

Research frontiers

The aim of this paper is to evaluate the impact of short and mid-term results of laparoscopy in liver surgery.

Innovations and breakthroughs

Minimally invasive approach represents the standard of care for most digestive cancer and it has to be confirmed for liver malignancies.

Applications

The extended indication for liver malignancies are even more frequent and need to be confirmed by short, middle and long term results.

Terminology

Minimally invasive and laparoscopic approach, liver resection, and better postoperative outcome are the main subjects of the paper.

Peer-review

This article has some important information to promote introduction of laparoscopy in the hepatobiliary and pancreatic field.

REFERENCES

- 1 Reich H, McGlynn F, DeCaprio J, Budin R. Laparoscopic excision of benign liver lesions. *Obstet Gynecol* 1991; **78**: 956-958 [PMID: 1833688]
- 2 Azagra JS, Goergen M, Gilbert E, Jacobs D. Laparoscopic anatomical (hepatic) left lateral segmentectomy-technical aspects. *Surg Endosc* 1996; **10**: 758-761 [PMID: 8662435 DOI: 10.1007/BF00193052]
- 3 John TG, Greig JD, Crosbie JL, Miles WF, Garden OJ. Superior staging of liver tumors with laparoscopy and laparoscopic ultrasound. *Ann Surg* 1994; **220**: 711-719 [PMID: 7986136 DOI: 10.1097/00000658-199412000-00002]
- 4 Rahusen FD, Cuesta MA, Borgstein PJ, Bleichrodt RP, Barkhof F, Doesburg T, Meijer S. Selection of patients for resection of colorectal metastases to the liver using diagnostic laparoscopy and laparoscopic ultrasonography. *Ann Surg* 1999; **230**: 31-37 [PMID: 10400033 DOI: 10.1097/00000658-199907000-00005]
- 5 Katkhouda N, Hurwitz M, Gugenheim J, Mavor E, Mason RJ, Waldrep DJ, Rivera RT, Chandra M, Campos GM, Offerman S, Trussler A, Fabiani P, Mouiel J. Laparoscopic management of benign solid and cystic lesions of the liver. *Ann Surg* 1999; **229**: 460-466 [PMID: 10203077 DOI: 10.1097/00000658-199904000-00003]
- 6 Morino M, De Giulio M, Festa V, Garrone C. Laparoscopic management of symptomatic nonparasitic cysts of the liver. Indications and results. *Ann Surg* 1994; **219**: 157-164 [PMID: 8129486 DOI: 10.1097/00000658-199402000-00007]
- 7 Descottes B, Lachachi F, Sodji M, Valleix D, Durand-Fontanier S, Pech de Laclause B, Grousseau D. Early experience with laparoscopic approach for solid liver tumors: initial 16 cases. *Ann Surg* 2000; **232**: 641-645 [PMID: 11066134 DOI: 10.1097/00000658-200011000-00004]
- 8 Cherqui D, Husson E, Hammoud R, Malassagne B, Stéphan F, Bensaid S, Rotman N, Fagniez PL. Laparoscopic liver resections: a feasibility study in 30 patients. *Ann Surg* 2000; **232**: 753-762 [PMID: 11088070 DOI: 10.1097/00000658-200012000-00004]
- 9 Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, Wakabayashi G, Belli G, Kaneko H, Ker CG, Scatton O, Laurent A, Abdalla EK, Chaudhury P, Dutson E, Gamblin C, D'Angelica M, Nagorney D, Testa G, Labow D, Manas D, Poon RT, Nelson H, Martin R, Clary B, Pinson WC, Martinie J, Vauthey JN, Goldstein R, Roayaie S, Barlet D, Espat J, Abecassis M, Rees M, Fong Y, McMasters KM, Broelsch C, Busuttil R, Belghiti J, Strasberg S, Chari RS. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 2009; **250**: 825-830 [PMID: 19916210 DOI: 10.1097/SLA.0b013e3181b3b2d8]
- 10 Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, Asbun H, O'Rourke N, Tanabe M, Koffron AJ, Tsung A, Soubrane O, Machado MA, Gayet B, Troisi RI, Pessaux P, Van Dam RM, Scatton O, Abu Hilal M, Belli G, Kwon CH, Edwin B, Choi GH, Aldrighetti LA, Cai X, Cleary S, Chen KH, Schön MR, Sugioka A, Tang CN, Herman P, Pekolj J, Chen XP, Dagher I, Jarnagin W, Yamamoto M, Strong R, Jagannath P, Lo CM, Clavien PA, Kokudo N, Barkun J, Strasberg SM. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015; **261**: 619-629 [PMID: 25742461 DOI: 10.1097/SLA.0000000000001184]
- 11 Tranchart H, Dagher I. Laparoscopic liver resection: a review. *J Visc Surg* 2014; **151**: 107-115 [PMID: 24365035 DOI: 10.1016/j.jviscsurg.2013.10.003]
- 12 Mala T, Edwin B, Gladhaug I, Fosse E, Søreide O, Bergan A, Mathisen O. A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. *Surg Endosc* 2002; **16**: 1059-1063 [PMID: 12165823 DOI: 10.1007/s00464-001-9176-5]
- 13 Are C, Fong Y, Geller DA. Laparoscopic liver resections. *Adv Surg* 2005; **39**: 57-75 [PMID: 16250546 DOI: 10.1016/j.yasu.2005.05.004]
- 14 Viganò L, Tayar C, Laurent A, Cherqui D. Laparoscopic liver resection: a systematic review. *J Hepatobiliary Pancreat Surg* 2009; **16**: 410-421 [PMID: 19495556 DOI: 10.1007/s00534-009-0120-8]
- 15 Couinaud C. [Definition of hepatic anatomical regions and their value during hepatectomy (author's transl)]. *Chirurgie* 1980; **106**: 103-108 [PMID: 7471968]
- 16 Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. *Ann Surg* 2013; **257**: 377-382 [PMID: 22895397 DOI: 10.1097/SLA.0b013e31825a01f6]
- 17 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
- 18 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187-196 [PMID: 19638912 DOI: 10.1097/SLA.0b013e3181b13ca2]
- 19 D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**: 2265-2281 [PMID: 9802183]
- 20 Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol* 2010; **172**: 1092-1097 [PMID: 20802241 DOI: 10.1093/aje/kwq224]
- 21 Steiner PM, Cook TD, Shadish WR, Clark MH. The importance of covariate selection in controlling for selection bias in observational studies. *Psychol Methods* 2010; **15**: 250-267 [PMID: 20822251 DOI: 10.1037/a0018719]
- 22 Dagher I, Franco D. [Right Hepatectomy by laparoscopic approach]. *J Chir (Paris)* 2007; **144**: 47-51 [PMID: 17369762 DOI: 10.1016/S0021-7697(07)89456-7]
- 23 Dagher I, Proske JM, Carloni A, Richa H, Tranchart H, Franco D. Laparoscopic liver resection: results for 70 patients. *Surg Endosc*

- 2007; **21**: 619-624 [PMID: 17285378 DOI: 10.1007/s00464-006-9137-0]
- 24 **Topal B**, Fieuw S, Aerts R, Vandeweyer H, Penninckx F. Laparoscopic versus open liver resection of hepatic neoplasms: comparative analysis of short-term results. *Surg Endosc* 2008; **22**: 2208-2213 [PMID: 18622562 DOI: 10.1007/s00464-008-0023-9]
 - 25 **Mala T**, Edwin B, Rosseland AR, Gladhaug I, Fosse E, Mathisen O. Laparoscopic liver resection: experience of 53 procedures at a single center. *J Hepatobiliary Pancreat Surg* 2005; **12**: 298-303 [PMID: 16133696]
 - 26 **Kaneko H**. Laparoscopic hepatectomy: indications and outcomes. *J Hepatobiliary Pancreat Surg* 2005; **12**: 438-443 [PMID: 16365815 DOI: 10.1007/s00534-005-1028-6]
 - 27 **Bryant R**, Laurent A, Tayar C, Cherqui D. Laparoscopic liver resection-understanding its role in current practice: the Henri Mondor Hospital experience. *Ann Surg* 2009; **250**: 103-111 [PMID: 19561476 DOI: 10.1097/SLA.0b013e3181ad6660]
 - 28 **Buell JF**, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV, Brock G, McMasters KM. Experience with more than 500 minimally invasive hepatic procedures. *Ann Surg* 2008; **248**: 475-486 [PMID: 18791368 DOI: 10.1097/SLA.0b013e318185e647]
 - 29 **Cho JY**, Han HS, Yoon YS, Shin SH. Experiences of laparoscopic liver resection including lesions in the posterosuperior segments of the liver. *Surg Endosc* 2008; **22**: 2344-2349 [PMID: 18528623 DOI: 10.1007/s00464-008-9966-0]
 - 30 **Vibert E**, Perniceni T, Levard H, Denet C, Shahri NK, Gayet B. Laparoscopic liver resection. *Br J Surg* 2006; **93**: 67-72 [PMID: 16273531 DOI: 10.1002/bjs.5150]
 - 31 **Cherqui D**. Laparoscopic liver resection. *Br J Surg* 2003; **90**: 644-646 [PMID: 12808610 DOI: 10.1002/bjs.4197]
 - 32 **Gayet B**, Cavaliere D, Vibert E, Perniceni T, Levard H, Denet C, Christidis C, Blain A, Mal F. Totally laparoscopic right hepatectomy. *Am J Surg* 2007; **194**: 685-689 [PMID: 17936436 DOI: 10.1016/j.amjsurg.2006.11.044]
 - 33 **Dagher I**, Caillard C, Proske JM, Carloni A, Lainas P, Franco D. Laparoscopic right hepatectomy: original technique and results. *J Am Coll Surg* 2008; **206**: 756-760 [PMID: 18387485 DOI: 10.1016/j.jamcollsurg.2007.09.012]
 - 34 **Salloum C**, Subar D, Memeo R, Tayar C, Laurent A, Malek A, Azoulay D. Laparoscopic robotic liver surgery: the Henri Mondor initial experience of 20 cases. *J Robot Surg* 2014; **8**: 119-124 [DOI: 10.1007/s11701-013-0437-9]
 - 35 **Memeo R**, Subar D, de'Angelis N, Salloum C, Azoulay D. A simple technique for procuring liver allografts while protecting arterial vessels. *Prog Transplant* 2014; **24**: 271-272 [PMID: 25193728 DOI: 10.7182/pit2014419]
 - 36 **Dagher I**, Gayet B, Tzanis D, Tranchart H, Fuks D, Soubrane O, Han HS, Kim KH, Cherqui D, O'Rourke N, Troisi RI, Aldrighetti L, Bjorn E, Abu Hilal M, Belli G, Kaneko H, Jarnagin WR, Lin C, Pekolj J, Buell JF, Wakabayashi G. International experience for laparoscopic major liver resection. *J Hepatobiliary Pancreat Sci* 2014; **21**: 732-736 [PMID: 25098667 DOI: 10.1002/jhbp.140]
 - 37 **Ishizawa T**, Gumbs AA, Kokudo N, Gayet B. Laparoscopic segmentectomy of the liver: from segment I to VIII. *Ann Surg* 2012; **256**: 959-964 [PMID: 22968066 DOI: 10.1097/SLA.0b013e31825ffed3]
 - 38 **Ogiso S**, Conrad C, Araki K, Nomi T, Anil Z, Gayet B. Laparoscopic Transabdominal With Transdiaphragmatic Access Improves Resection of Difficult Posterosuperior Liver Lesions. *Ann Surg* 2015; **262**: 358-365 [PMID: 25848711 DOI: 10.1097/SLA.0000000000001015]
 - 39 **Hallet J**, Soler L, Diana M, Mutter D, Baumert TF, Habersetzer F, Marescaux J, Pessaux P. Trans-thoracic minimally invasive liver resection guided by augmented reality. *J Am Coll Surg* 2015; **220**: e55-e60 [PMID: 25840539 DOI: 10.1016/j.jamcollsurg.2014.12.053]
 - 40 **Elias D**, Desruennes E, Lasser P. Prolonged intermittent clamping of the portal triad during hepatectomy. *Br J Surg* 1991; **78**: 42-44 [PMID: 1998862 DOI: 10.1002/bjs.1800780115]
 - 41 **Wu CC**, Hwang CR, Liu TJ, P'eng FK. Effects and limitations of prolonged intermittent ischaemia for hepatic resection of the cirrhotic liver. *Br J Surg* 1996; **83**: 121-124 [PMID: 8653335 DOI: 10.1002/bjs.1800830139]
 - 42 **Belghiti J**, Noun R, Malafosse R, Jagot P, Sauvanet A, Pierangeli F, Marty J, Farges O. Continuous versus intermittent portal triad clamping for liver resection: a controlled study. *Ann Surg* 1999; **229**: 369-375 [PMID: 10077049 DOI: 10.1097/00000658-199903000-00010]
 - 43 **De Carlis L**, Di Sandro S, Giacomoni A, Mihaylov P, Lauterio A, Mangoni I, Cusumano C, Poli C, Tripepi M, Bencardino K. Colorectal liver metastases: Hepatic pedicle clamping during hepatectomy reduces the incidence of tumor recurrence in selected patients. Case-matched analysis. *Eur J Surg Oncol* 2013; **39**: 726-733 [PMID: 23601983 DOI: 10.1016/j.ejso.2013.03.015]
 - 44 **Bazin JE**, Gillart T, Rasson P, Conio N, Aigouy L, Schoeffler P. Haemodynamic conditions enhancing gas embolism after venous injury during laparoscopy: a study in pigs. *Br J Anaesth* 1997; **78**: 570-575 [PMID: 9175974 DOI: 10.1093/bja/78.5.570]
 - 45 **Palmer M**, Miller CW, van Way CW, Orton EC. Venous gas embolism associated with argon-enhanced coagulation of the liver. *J Invest Surg* 1993; **6**: 391-399 [PMID: 8292567]
 - 46 **Fuks D**, Cauchy F, Férêche S, Nomi T, Schwarz L, Dokmak S, Scatton O, Fusco G, Belghiti J, Gayet B, Soubrane O. Laparoscopy Decreases Pulmonary Complications in Patients Undergoing Major Liver Resection: A Propensity Score Analysis. *Ann Surg* 2016; **263**: 353-361 [PMID: 25607769 DOI: 10.1097/SLA.0000000000001140]
 - 47 **Han HS**, Shehta A, Ahn S, Yoon YS, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: Case-matched study with propensity score matching. *J Hepatol* 2015; **63**: 643-650 [PMID: 25872167 DOI: 10.1016/j.jhep.2015.04.005]
 - 48 **Takahara T**, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, Hatano E, Tanahashi Y, Mizuguchi T, Kamiyama T, Ikeda T, Tanaka S, Taniai N, Baba H, Tanabe M, Kokudo N, Konishi M, Uemoto S, Sugioka A, Hirata K, Taketomi A, Maehara Y, Kubo S, Uchida E, Miyata H, Nakamura M, Kaneko H, Yamaue H, Miyazaki M, Takada T. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. *J Hepatobiliary Pancreat Sci* 2015; **22**: 721-727 [PMID: 26096910 DOI: 10.1002/jhbp.276]
 - 49 **de'Angelis N**, Memeo R, Calderaro J, Felli E, Salloum C, Compagnon P, Luciani A, Laurent A, Cherqui D, Azoulay D. Open and laparoscopic resection of hepatocellular adenoma: trends over 23 years at a specialist hepatobiliary unit. *HPB (Oxford)* 2014; **16**: 783-788 [PMID: 24852081 DOI: 10.1111/hpb.12257]
 - 50 **Cannon RM**, Scoggins CR, Callender GG, McMasters KM, Martin RC. Laparoscopic versus open resection of hepatic colorectal metastases. *Surgery* 2012; **152**: 567-573; discussion 573-574 [PMID: 22943842 DOI: 10.1016/j.surg.2012.07.013]
 - 51 **Simillis C**, Constantinides VA, Tekkis PP, Darzi A, Lovegrove R, Jiao L, Antoniou A. Laparoscopic versus open hepatic resections for benign and malignant neoplasms--a meta-analysis. *Surgery* 2007; **141**: 203-211 [PMID: 17263977 DOI: 10.1016/j.surg.2006.06.035]

P- Reviewer: Ogiso S, Toriguchi K, Wakabayashi G, Zhao HT

S- Editor: Gong ZM **L- Editor:** A **E- Editor:** Li D



Retrospective Study

Barium appendicitis: A single institution review in Japan

Hideki Katagiri, Alan Kawai Lefor, Tadao Kubota, Ken Mizokami

Hideki Katagiri, Tadao Kubota, Ken Mizokami, Department of Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu city, Chiba 279-0001, Japan

Alan Kawai Lefor, Department of Surgery, Jichi Medical University, Shimotsuke, Tochigi 329-0498, Japan

Author contributions: Katagiri H and Lefor AK were major contributors in writing manuscript; Katagiri H, Kubota T and Mizokami K collected and analyzed the data, and designed this study; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Tokyo Bay Urayasu Ichikawa Medical Center Institutional Review Board.

Informed consent statement: Written informed consent was obtained from the patients whose images are used in this study for publication of this study and accompanying images.

Conflict-of-interest statement: All authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Hideki Katagiri, MD, Department of Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, 3-4-32, Todaijima, Urayasu city, Chiba 279-0001, Japan. x62h20k38@yahoo.co.jp
Telephone: +81-047-3513101
Fax: +81-047-3526237

Received: April 25, 2016

Peer-review started: April 26, 2016

First decision: June 16, 2016

Revised: July 8, 2016

Accepted: July 20, 2016

Article in press: July 22, 2016

Published online: September 27, 2016

Abstract**AIM**

To review clinical experience with barium appendicitis at a single institution.

METHODS

A retrospective review of patients admitted with a diagnosis of acute appendicitis, from January 1, 2013 to December 31, 2015 was performed. Age, gender, computed tomography (CT) scan findings if available, past history of barium studies, pathology, and the presence of perforation or the development of complications were reviewed. If the CT scan revealed high density material in the appendix, the maximum CT scan radiodensity of the material is measured in Hounsfield units (HU). Barium appendicitis is defined as: (1) patients diagnosed with acute appendicitis; (2) the patient has a history of a prior barium study; and (3) the CT scan shows high density material in the appendix. Patients who meet all three criteria are considered to have barium appendicitis.

RESULTS

In total, 396 patients were admitted with the diagnosis of acute appendicitis in the study period. Of these, 12 patients (3.0%) met the definition of barium appendicitis. Of these 12 patients, the median CT scan radiodensity of material in the appendix was 10000.8 HU, ranging from 3066 to 23423 HU (\pm 6288.2). In contrast, the median CT scan radiodensity of fecaliths in the appendix, excluding patients with barium appendicitis, was 393.1 HU, ranging from 98 to 2151 HU (\pm 382.0). The CT scan radiodensity of material in the appendices of patients with barium appendicitis was

significantly higher than in patients with nonbarium fecaliths ($P < 0.01$).

CONCLUSION

Barium appendicitis is not rare in Japan. Measurement of the CT scan radiodensity of material in the appendix may differentiate barium appendicitis from routine appendicitis.

Key words: Acute appendicitis; Barium appendicitis; Barium sulfate; Upper gastrointestinal imaging; Gastric cancer screening

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This is a retrospective study to review clinical experience with barium appendicitis at a single institution in Japan. In the three years of study period, 12 patients (3.0%) were diagnosed as barium appendicitis among 396 patients with acute appendicitis. The computed tomography (CT) scan radiodensity of material in the appendices of patients with barium appendicitis was significantly higher than in patients with nonbarium fecaliths. Barium appendicitis is not rare in Japan. Measurement of the CT scan radiodensity of material in the appendix may differentiate barium appendicitis from routine appendicitis.

Katagiri H, Lefor AK, Kubota T, Mizokami K. Barium appendicitis: A single institution review in Japan. *World J Gastrointest Surg* 2016; 8(9): 651-655 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/651.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.651>

INTRODUCTION

Acute appendicitis is one of the most common surgical problems encountered in clinical surgical practice. While the exact etiology of acute appendicitis remains unclear, an obstruction of the appendiceal lumen can result in the development of acute appendicitis^[1]. In Japan, upper gastrointestinal imaging using barium sulfate is widely used in mass screening programs for gastric cancer^[2]. Barium sulfate is not harmful to the intestinal mucosa and complications after a barium study are considered to be very rare^[2-4]. Acute appendicitis caused by residual barium is also thought to be a very rare complication after a barium study^[3-5]. General surgeons in Japan often encounter patients with acute appendicitis who have residual barium felt to be the responsible etiologic agent.

We performed a retrospective review of patients admitted with a diagnosis of acute appendicitis, and specifically reviewed those with acute appendicitis suspected to be caused by residual barium.

MATERIALS AND METHODS

Tokyo Bay Urayasu Ichikawa Medical Center is a secondary referral hospital in Chiba prefecture, Japan, providing acute surgical care. A retrospective analysis was conducted of patients seen from January 1, 2013 to December 31, 2015. Patients for review were identified based on their medical records including patients admitted with the diagnosis of acute appendicitis. Age, gender, computed tomography (CT) scan findings if available, past history of barium studies, pathology, and the presence of perforation or the development of complications were reviewed. If the CT scan revealed high density material in the appendix, the maximum CT scan radiodensity of the material is measured in Hounsfield units (HU).

Barium appendicitis is defined as: (1) patients diagnosed with acute appendicitis; (2) the patients have a history of a prior barium study; and (3) the CT scan shows high density material in the appendix. Patients who meet all three criteria are considered to have barium appendicitis.

Data were analyzed with Fisher's exact test and the Mann-Whitney *U* test. A *P*-value less than 0.05 is considered statistically significant.

RESULTS

From January 1, 2013 to December 31, 2015, 396 patients were admitted with the diagnosis of acute appendicitis, including 210 males and 186 females. The median age is 37 years, ranging from 5 to 86 years. Of these, 12 patients (3.0%) met the definition of barium appendicitis (Table 1, Figure 1), including ten males and two females, with a median age of 48 years, ranging from 37 to 62 years. Of these 12 patients, the median CT scan radiodensity of material in the appendix was 10000.8 HU, ranging from 3066 to 23423 HU (± 6288.2). According to these data, the CT scan radiodensity of residual barium is generally higher than 3000 HU. If we apply this value as a cutoff, we can identify seven more patients with suspected barium appendicitis based on CT scan radiodensity alone. According to the medical records, these seven patients had no definite history of a preceding barium study, excluding one patient who specifically denied having a barium study. The median CT scan radiodensity of fecaliths in the appendix, excluding patients with barium appendicitis, was 393.1 HU, ranging from 98 to 2151 HU (± 382.0). The CT scan radiodensity of material in patients with barium appendicitis was significantly higher than patients with non-barium fecaliths ($P < 0.01$).

Ten of 12 patients with barium appendicitis underwent laparoscopic appendectomy urgently. One patient underwent interval laparoscopic appendectomy after initially successful non-operative management. In one patient, there was obvious perforation with abscess formation and non-operative management was initially undertaken. Following this, the patient refused interval appendectomy. The interval from barium study to the diagnosis of appendicitis was variable, ranging from 2 d to 10 mo.

The pathological results in patients with barium appen-

Table 1 Patient characteristics

Age	Gender	Maximum CT density (HU)	Perforation	Appendix pathology	Interval between barium study and diagnosis	Treatment
52	M	10243	+	Phlegmonous	8 mo	Laparoscopic appendectomy
37	M	23423	-	Gangrenous	2 d	Laparoscopic appendectomy
45	M	6620	-	Gangrenous	1 mo	Laparoscopic appendectomy
49	M	15286	-	Phlegmonous	16 d	Laparoscopic appendectomy
44	M	3066	-	Gangrenous	1 mo	Laparoscopic appendectomy
62	M	18286	+	Gangrenous	Not documented	Laparoscopic appendectomy
45	M	8192	+	Chronic appendicitis	3 mo	Primary non-operative management followed by interval appendectomy
46	M	11514	-	Phlegmonous	10 mo	Laparoscopic appendectomy
60	F	3178	-	Gangrenous	Not documented	Laparoscopic appendectomy
44	M	8727	-	Gangrenous	3 mo	Laparoscopic appendectomy
45	M	7806	-	Gangrenous	5 mo	Laparoscopic appendectomy
41	F	3669	+	N/A	1 mo	Non-operative management without interval appendectomy

M: Male; F: Female; CT: Computed tomography; HU: Hounsfield units; N/A: Not analyzed.

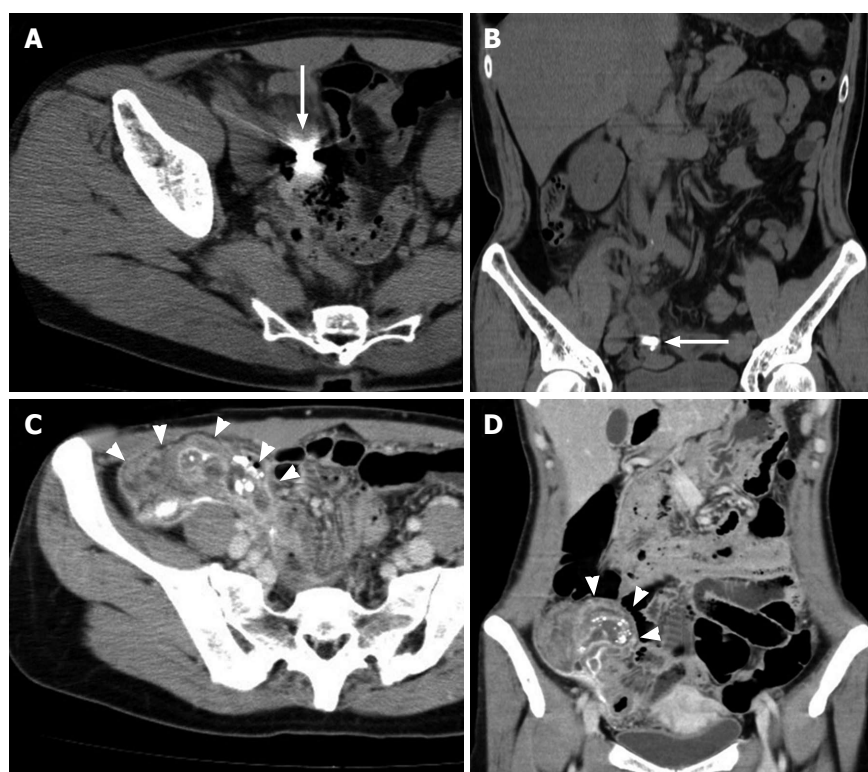


Figure 1 Abdominal computed tomography scans with axial and coronal views. A and B: High density material is seen inside the swollen appendix (arrows); C and D: High density material is seen inside the swollen appendix and in the peritoneal cavity with a fluid collection (arrow heads). This strongly suggests a perforated appendicitis with residual barium.

ditis are available for 11 patients. Seven patients had gangrenous appendicitis and three had phlegmonous appendicitis. One patient, who underwent interval appendectomy, had chronic inflammation of the appendix. The rate of gangrenous appendicitis is 58.3% in patients with barium appendicitis and 56.4% in patients without barium appendicitis. The rate of gangrenous appendicitis is almost the same in patients with typical (unassociated with barium) appendicitis compared to patients with barium appendicitis. Four out of 12 patients had a perforation (33.3%), confirmed by intraoperative or imaging findings. The perforation rate in patients with

barium appendicitis was higher than in patients without barium appendicitis (18.8% in this study), which is not statistically significant ($P = 0.25$). Interestingly, although the rate of gangrenous appendicitis is almost the same in patients with barium appendicitis and typical appendicitis the perforation rate was higher in patients with barium appendicitis.

DISCUSSION

Barium appendicitis is a rare complication after barium examinations and was first described by Gubler *et al*^[6]

in 1954. Although retained barium in the appendix after barium studies is very common^[7], especially after colon studies, more than 90% of patients evacuate the barium within 72 h^[3,4,7]. The true pathophysiology of barium appendicitis remains unclear. The true incidence of barium appendicitis is also unknown because only a few case reports or small case series have been reported to date^[3-7]. The time interval between the barium study and the diagnosis of barium appendicitis in several previous studies ranges from four hours to four years^[5,8]. In the present study, the range is 10 d to 10 mo. The wide range of values suggests that retained barium in the appendix alone does not result in appendicitis. There would appear to be other factors that contribute to the development of acute appendicitis.

Acute appendicitis is one of the most common surgical emergencies encountered by general surgeons. Obstruction of the appendiceal lumen, often due to a fecalith, lymphoid hyperplasia, or rarely a cecal or appendiceal tumor, is generally thought to be the cause of acute appendicitis in many patients^[1,9]. Fecaliths are a cause of obstruction of the appendiceal lumen, although they are not always found at surgery. Fecaliths are composed of inspissated stool, mucus with trapped calcium phosphate and inorganic salts, which finally obstructs the appendiceal lumen^[10,11]. In this study, fecaliths were identified in 34% of patients with acute appendicitis based on imaging findings. It is unknown if the high density material in the appendix in patients with barium appendicitis is composed of only barium or if it is combined with other material such as that found in a fecalith. However, luminal obstruction of the appendix by residual barium resulted in the development of acute appendicitis. As mentioned, an additional cause of barium appendicitis may be a pre-existing fecalith in the appendix. Fecaliths not only cause appendicitis, but also are considered to be associated with appendiceal perforation^[11,12]. In this study, the perforation rate in patients with barium appendicitis was higher than in patients without barium appendicitis. Although it is not statistically significant, this suggests that residual barium may be a risk factor for appendiceal perforation, similar to a fecalith. The fact that typical appendicitis has the same rate of gangrenous inflammation in this study also supports this hypothesis.

In this study, the CT scan radiodensity of material in the appendix in patients with barium appendicitis is significantly higher than that of fecaliths in patients with typical appendicitis. These data suggest that the CT scan radiodensity of material in the appendix may differentiate barium from normal fecaliths. We acknowledge that in general, not all patients undergo CT scans to establish the diagnosis of acute appendicitis. However, during the study period, about 3% of patients presented with acute appendicitis believed to be caused by residual barium. Since acute appendicitis is one of the most common surgical emergencies, and the fact that in Japan, barium is widely used in studies screening for gastric cancer^[2], we believe that the diagnosis and recognition of barium

appendicitis as a complication of barium studies is worthwhile, especially in Japan.

According to data reporting the complications after gastric cancer screening in Japan, the total complication rate after barium studies is reported to be less than 0.04%^[13]. The most common reported complication after barium studies was aspiration, followed by allergic reaction and bowel obstruction. There have also been severe complications reported such as intestinal perforation due to residual barium^[13]. Interestingly, there were no reports of barium appendicitis^[13], although barium appendicitis occurred in 3% of patients with acute appendicitis in this study. There is an approximate 7% lifetime risk of developing appendicitis^[1,9], thus, a 3% incidence in patients with acute appendicitis is a significant number. Since acute appendicitis is often treated with appendectomy no matter what the etiology, the true incidence of barium appendicitis is likely underestimated.

Several limitations are acknowledged in this study. First, this is a single institution retrospective analysis. Second, there is no confirmation of what the high density material in the resected appendices actually was. Pathological confirmation may support the results of this study, if it is specifically checked in a prospective study.

In conclusion, barium appendicitis is not rare in Japan. Measurement of the CT scan radiodensity of material in the appendix may differentiate barium appendicitis from routine appendicitis. Since barium is widely used in Japan for gastric cancer screening, determination of the true incidence of barium appendicitis is important.

This material was presented in part at the 116th annual congress of the Japan Surgical Society (April 15th 2016, Osaka, Japan).

COMMENTS

Background

Barium appendicitis is a rare complication of gastrointestinal imaging using barium sulfate. The true incidence of barium appendicitis is unknown. However, general surgeons in Japan often encounter patients with acute appendicitis where the etiology appears to be a barolith in the appendix. The authors review their clinical experience with barium appendicitis at a single institution in Japan.

Research frontiers

The exact incidence of barium appendicitis is unknown. This study reviews their experience with appendicitis and the incidence of barium appendicitis among all patients who presented with acute appendicitis.

Innovations and breakthroughs

Barium appendicitis is thought to be a rare complication of gastrointestinal imaging. However, this study shows that barium appendicitis represents about 3% of all patients with acute appendicitis.

Applications

Measurement of the computed tomography (CT) scan radiodensity of high density material in the appendix may help to differentiate barium appendicitis from typical appendicitis. This may also help elucidate the true incidence of barium appendicitis in future studies.

Terminology

HU: Hounsfield units.

Peer-review

Barium appendicitis is a rare clinical condition. Barolith can occur due to post-examination retained barium in appendix lumen and it can cause appendicitis. CT definings in this manuscript is well-thought evidence and helps diagnose.

REFERENCES

- 1 **Bhangu A**, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet* 2015; **386**: 1278-1287 [PMID: 26460662 DOI: 10.1016/S0140-6736(15)00275-5]
- 2 **Hamashima C**, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008; **38**: 259-267 [PMID: 18344316 DOI: 10.1093/jjco/hyn017]
- 3 **Urade M**, Shinbo T. Barium appendicitis 1 month after a barium meal. *Int Surg* 2012; **97**: 296-298 [PMID: 23294068 DOI: 10.9738/CC160.1]
- 4 **Fang YJ**, Wang HP, Ho CM, Liu KL. Barium appendicitis. *Surgery* 2009; **146**: 957-958 [PMID: 19744430 DOI: 10.1016/j.surg.2008.05.021]
- 5 **Novotny NM**, Lillemoe KD, Falimirski ME. Barium appendicitis after upper gastrointestinal imaging. *J Emerg Med* 2010; **38**: 148-149 [PMID: 18842384 DOI: 10.1016/j.jemermed.2008.04.017]
- 6 **Gubler JA**, Kukral AJ. Barium appendicitis. *J Int Coll Surg* 1954; **21**: 379-384 [PMID: 13143262]
- 7 **Maglinte DD**, Bush ML, Aruta EV, Bullington GE. Retained barium in the appendix: diagnostic and clinical significance. *AJR Am J Roentgenol* 1981; **137**: 529-533 [PMID: 6974465 DOI: 10.2214/ajr.137.3.529]
- 8 **Cohen N**, Modai D, Rosen A, Golik A, Weissgarten J. Barium appendicitis: fact or fancy? Report of a case and review of the literature. *J Clin Gastroenterol* 1987; **9**: 447-451 [PMID: 3309023]
- 9 **Engin O**, Muratli A, Ucar AD, Tekin V, Calik B, Tosun A. The importance of fecaliths in the aetiology of acute appendicitis. *Chirurgia (Bucur)* 2012; **107**: 756-760 [PMID: 23294954]
- 10 **Maatouk M**, Bunni J, Schuijtvlot M. Perihepatic abscess secondary to retained appendicolith: A rare complication managed laparoscopically. *J Surg Case Rep* 2011; **2011**: 6 [PMID: 24950544 DOI: 10.1093/jscr/2011.1.6]
- 11 **Alaudeen DI**, Cook M, Chwals WJ. Appendiceal fecalith is associated with early perforation in pediatric patients. *J Pediatr Surg* 2008; **43**: 889-892 [PMID: 18485960 DOI: 10.1016/j.jpedsurg.2007.12.034]
- 12 **Singh JP**, Mariadason JG. Role of the faecolith in modern-day appendicitis. *Ann R Coll Surg Engl* 2013; **95**: 48-51 [PMID: 23317728 DOI: 10.1308/003588413X13511609954851]
- 13 **Shibuya D**, Ishikawa T, Ichinose M, Iriguchi Y, Kitagawa S, Tobori F, et.al. Annual report of complications related to gastric cancer screening: results of the Japanese Society of Gastrointestinal Cancer Screening survey from April 1, 2012 to March 31, 2013. (Title and article in Japanese). *J Gastrointestinal Cancer Screen*. 2015; **53**: 233-238 [DOI: 10.11404/jsgcs.53.233]

P- Reviewer: Charfi S, Ince V **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Li D



Eosinophilic ascites: A diagnostic and therapeutic challenge

Shefali Agrawal, Sandeep Vohra, Sangeeta Rawat, Vikas Kashyap

Shefali Agrawal, Hepatobiliary and Pancreatic Surgery, Department of Surgical Oncology, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110076, India

Sandeep Vohra, Department of Radiology, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110076, India

Sangeeta Rawat, Vikas Kashyap, Department of Pathology, Indraprastha Apollo Hospitals, Sarita Vihar, New Delhi 110076, India

Author contributions: Agrawal S contributed to study conception and design and drafting of manuscript; Agrawal S, Vohra S, Rawat S and Kashyap V contributed to acquisition of data and critical revision.

Institutional review board statement: As per our institutional policy, permission by the Institutional review board is not required for publication of case reports.

Informed consent statement: As per our institutional policy, once all information pertaining to the unique markers of the patient's identity have been deleted from the case report an informed consent from the patient is not necessary.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Shefali Agrawal, MD, MS, FACS, Senior Consultant, Hepatobiliary and Pancreatic Surgery, Department of Surgical Oncology, Indraprastha Apollo Hospitals, Delhi Mathura Road, Sarita Vihar, New Delhi 110076, India. shefali_a@apollohospitals.com
Telephone: +91-81-30009660

Received: May 24, 2016

Peer-review started: May 25, 2016

First decision: July 6, 2016

Revised: July 12, 2016

Accepted: July 29, 2016

Article in press: August 1, 2016

Published online: September 27, 2016

Abstract

Eosinophilic gastroenteritis (EGE) is a rare condition characterized by eosinophilic infiltration of the gastrointestinal tract. Depending on the dominant layer of infiltration it is classified into three types namely, mucosal, muscularis and subserosal. The most uncommon variant is the subserosal type characterized by primarily subserosal disease, eosinophilic ascites and peripheral hypereosinophilia. The clinical features are non-specific with history of atopic predisposition and allergy. Endoscopic biopsy is frequently non-diagnostic due to an uninvolved gastrointestinal mucosa rendering its diagnosis a challenge. The mainstay of diagnosis is peripheral hypereosinophilia and eosinophil-rich ascitic fluid on diagnostic paracentesis. Oral steroid therapy is usually the first line of treatment with dramatic response. Due to a propensity for relapse, steroid-sparing therapy should be considered for relapses of EGE. We report a case of subserosal EGE with diagnostic clinical features and treatment response and review the current strategy in the management of eosinophilic ascites.

Key words: Gastrointestinal; Atopy; Eosinophilic ascites; Endoscopic biopsy; Eosinophilia

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Eosinophilic gastroenteritis (EGE) is a rare condition and the diagnosis of subserosal EGE is challenging due to its nonspecific symptoms and signs and frequently non-diagnostic biopsy on gastrointestinal endoscopy. This review describes a patient with typical findings of peripheral hypereosinophilia and eosinophilic

ascites and outlines the current strategy in the diagnosis and treatment of subserosal EGE.

Agrawal S, Vohra S, Rawat S, Kashyap V. Eosinophilic ascites: A diagnostic and therapeutic challenge. *World J Gastrointest Surg* 2016; 8(9): 656-659 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i9/656.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i9.656>

INTRODUCTION

Eosinophilic gastroenteritis (EGE) is a rare and potentially fatal condition with clinico-pathologic characteristics of peripheral hypereosinophilia and eosinophilic infiltration of the gastrointestinal tract. It is classified into three pathologic types depending on the dominant gastrointestinal layer of eosinophilic infiltration^[1]. The subserosal type characterized by primarily subserosal disease and eosinophilic ascites is the rarest presentation of EGE^[2,3]. Biopsy of the mucosal layer obtained during upper gastrointestinal endoscopy frequently fails to diagnose subserosal EGE. The diagnosis of subserosal EGE is challenging because of its rarity, nonspecific clinical presentation and non-diagnostic endoscopy. This study presents the typical clinico-pathologic and radiologic findings in subserosal EGE and reviews the current diagnostic and therapeutic strategy in patients with abdominal pain, ascites and peripheral hypereosinophilia.

CASE REPORT

A 35-year-old female presented to the clinic with complaints of abdominal distension and an episode of self-limiting diarrhea three weeks ago. She admitted to the recent use of green tea and increased consumption of nuts in her diet. Past medical history was remarkable for recurrent allergic bronchitis. On examination there was no evidence of pallor, icterus or peripheral edema and abdominal examination revealed moderate distention with a doughy consistency. Abdominal ultrasonography demonstrated moderate ascites with no signs of portal hypertension, liver or renal disease. Contrast-enhanced abdominal computed tomography confirmed the presence of free peritoneal fluid, diffuse circumferential thickening of small bowel loops, distal stomach and esophagus (Figure 1). Laboratory examination revealed peripheral eosinophilic leukocytosis with 52% eosinophils (total leukocyte count 22900 cells/mm³) and no immature myeloid precursors. The C-reactive protein, erythrocyte sedimentation rate and IgE levels were within normal limits. Tumor marker CA-125 was normal. Skin prick test results for food allergens and stool examination for bacteria, ova and parasites were negative. Diagnostic paracentesis was moderately cellular with 100% eosinophils, negative for malignant cells and sterile (Figure 2). Upper endoscopy and colonoscopy demonstrated mild erythema of the gastric antrum with an unremarkable

esophagus, duodenum, colon and terminal ileum. Histology revealed a mild inflammatory infiltrate in the lamina propria of the gastric antrum and duodenum comprising of lymphocytes, plasma cells and scattered eosinophils (Figure 3). Echocardiographic findings were normal. Bone marrow aspiration and biopsy showed hypercellularity with a marked increase in mature eosinophils without blasts. The findings confirmed a diagnosis of subserosal EGE.

The patient was treated with oral prednisone 25 mg daily with rapid symptomatic improvement and normalization of the hypereosinophilia within a week of initiation of steroid therapy. Four months after the weaning of steroids, follow-up abdominal computed tomography demonstrated complete resolution of the peritoneal fluid and bowel wall thickening. Two years after completion of therapy, the patient remains asymptomatic and free of ascites or hypereosinophilia.

DISCUSSION

EGE is a rare disease with an estimated prevalence of 28/100000 in United States^[4]. Klein *et al*^[1] classified EGE into three types based on the dominant layer of eosinophilic infiltration (1) predominant mucosal disease characterized by iron deficiency anemia, protein-losing enteropathy and malabsorption; (2) predominant muscle layer disease characterized by localized or diffuse thickening of the bowel wall with features of pyloric narrowing and obstructive symptoms; and (3) predominant subserosal disease characterized by eosinophil-rich ascites^[1-5]. Mucosal EGE is the most common type (70%) followed by muscularis (20%) and subserosal (10%)^[6,7]. EGE may also present with obstructive jaundice due to biliary tract involvement or extraintestinal manifestations such as eosinophilic cystitis, eosinophilic splenitis and hepatitis^[7-9].

Talley *et al*^[10] have defined three diagnostic criteria for EGE (1) presence of gastrointestinal symptoms; (2) biopsies of the gastrointestinal tract showing eosinophilic infiltration or characteristic radiologic findings with peripheral eosinophilia or eosinophil-rich ascites with; and (3) no evidence of parasitic or extraintestinal disease. Characteristic findings of EGE on abdominal computed tomography include thickening of bowel wall or fold, layering of the bowel wall, luminal narrowing without obstruction, intra- or extra-luminal granuloma, mesenteric lymphadenopathy with peripheral rim-like enhancement or necrosis and ascites^[11]. The etiology of EGE is unclear however, an atopic predisposition is noted in patients with EGE with a history of allergy reported in 50% patients with EGE^[10]. A genetic predisposition is suspected as 16% of patients with EGE have a family member with a similar condition^[9]. The majority of the patients diagnosed with EGE are 20-50 years of age with no reported gender predisposition^[3].

The differential diagnosis of eosinophilic ascites includes parasitic infection (*Strongyloides stercoralis*, *Toxocara canis*), abdominal tuberculosis, rupture of hydatid cyst, chronic pancreatitis, vasculitis (Churg-Strauss

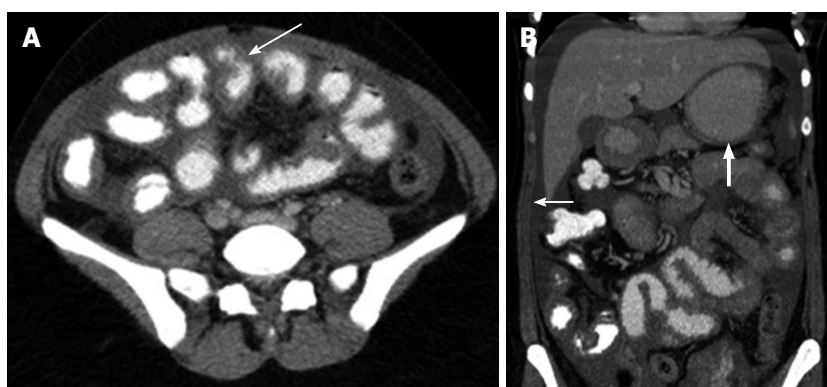


Figure 1 Findings on contrast-enhanced abdominal computed tomography. A: Sagittal section demonstrates thickened loops of small bowel (arrow); B: Coronal image demonstrates free peritoneal fluid (arrow), thickened loops of small bowel and circumferential mural thickening of the distal stomach (heavy arrow).

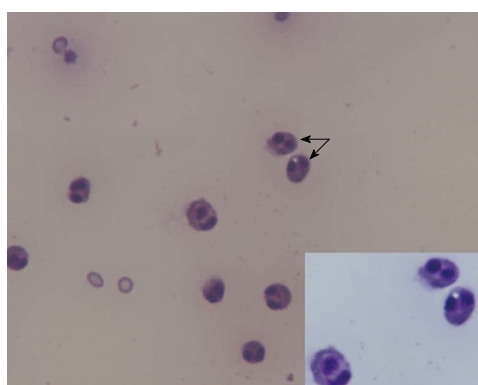


Figure 2 Diagnostic paracentesis demonstrates ascitic fluid rich in eosinophils (arrow), magnification 10 ×. Inset, eosinophils in ascitic fluid, May Grunwald Giemsa, magnification 100 ×.

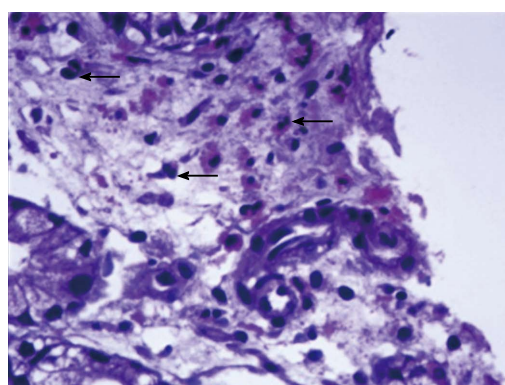


Figure 3 Endoscopic biopsy of gastric mucosa demonstrates scattered eosinophils (arrows) in the lamina propria. Hematoxylin and eosin, magnification 40 ×.

syndrome), hypereosinophilic syndrome, malignancy and Crohn's disease^[12]. The diagnosis of subserosal EGE remains challenging because of its rarity and non-specific clinical features. The most common clinical features include abdominal pain (90.4%), nausea and vomiting (57.1%), diarrhea (52.3%) and abdominal distension (38.1%)^[13]. It should be considered in the diagnostic evaluation of patients with abdominal pain, ascites and peripheral hypereosinophilia and a high index of suspicion should be maintained by the physician^[3]. The mainstay of diagnosis of subserosal EGE is confirmation of eosinophil-rich ascitic fluid on diagnostic paracentesis and peripheral hypereosinophilia.

The overall prognosis of EGE is good with an excellent response to oral steroids comprising the first line of therapy^[2]. Prednisone 20-40 mg daily in divided doses is highly effective with symptomatic remission in 80% patients within a week and normalization of eosinophil counts within two weeks of initiation of therapy^[13]. Other medical therapy includes antihistaminic drugs, sodium cromoglycate, montelukast and ketotifen^[2,12,14,15]. Ketotifen an antihistaminic drug and mast cell stabilizer has been used to successfully treat eosinophilic ascites as the sole therapeutic intervention. Casella *et al*^[15] recommend ketotifen as the first-line approach to eosinophilic ascites because it is a relatively inexpensive and safe drug. Sur-

gical intervention is rare and reserved for patients with obstructive complications^[2,3]. The clinical course may be characterized by periods of remission and relapses usually when the steroid therapy is discontinued in up to 50% patients^[14]. Steroid-sparing therapy with anti-histamines, mast cell inhibitors, leukotriene receptor antagonists, anti-interleukin drugs including ketotifen is useful in the treatment of relapses to avoid the side-effects of steroids^[12,15]. In rare cases of failure to respond to steroid therapy, total parenteral nutrition or immunosuppressive agents including oral azathioprine or cyclophosphamide may be added to the steroid regimen in patients with diffuse mucosal disease^[5].

COMMENTS

Case characteristics

A 35-year-old female presented with abdominal distension and diarrhea and was diagnosed with subserosal eosinophilic gastroenteritis (EGE). She responded to oral steroid therapy with complete resolution of the ascites and normalization of peripheral hypereosinophilia.

Clinical diagnosis

Subserosal EGE.

Differential diagnosis

Ovarian cancer, abdominal tuberculosis, vasculitis, parasitic infection, congestive

heart failure.

Laboratory diagnosis

Peripheral hypereosinophilia and eosinophil-rich fluid on diagnostic paracentesis.

Imaging diagnosis

Abdominal computed tomography demonstrated moderate ascites with diffuse wall thickening of the small bowel.

Pathological diagnosis

Mucosal biopsy of the stomach and duodenum on upper endoscopy was non-diagnostic.

Treatment

Oral steroid therapy.

Experiences and lessons

A high index of suspicion of subserosal EGE in patients with abdominal pain, ascites and peripheral hypereosinophilia. Oral steroids adequate for initial therapy and ketotifen may be considered for relapse of EGE.

Peer-review

The manuscript deals with a case report and a review on an important condition and is well written.

REFERENCES

- 1 Klein NC, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine* (Baltimore) 1970; **49**: 299-319 [PMID: 5426746 DOI: 10.1097/00005792-197007000-00003]
- 2 Antonini F, Saltarelli P, Frieri G, Latella G. Education and Imaging: gastrointestinal: eosinophilic ascites. *J Gastroenterol Hepatol* 2012; **27**: 1759 [PMID: 23106369 DOI: 10.1111/j.1440-1746.2012.07254.x]
- 3 Jarry J, Peycru T, Shekher M. A rare cause of ascites. *Gastroenterology* 2011; **140**: 1149, 1364 [PMID: 21352871 DOI: 10.1053/j.gastro.2010.05.095]
- 4 Spergel JM, Book WM, Mays E, Song L, Shah SS, Talley NJ, Bonis PA. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. *J Pediatr Gastroenterol Nutr* 2011; **52**: 300-306 [PMID: 21057327 DOI: 10.1097/MPG.0b013e3181eb5a9f]
- 5 Triantafyllidis JK, Parasi A, Cherakakis P, Sklavaina M. Eosinophilic gastroenteritis: Current aspects on etiology, pathogenesis, diagnosis and treatment. *Ann Gastroenterol* 2007; **15**: 106-115
- 6 Simoniuk U, McManus C, Kiire C. Eosinophilic gastroenteritis--a diagnostic enigma. *BMJ Case Rep* 2012; **2012** [PMID: 22891016 DOI: 10.1136/bcr.2011.5436]
- 7 Baig MA, Qadir A, Rasheed J. A review of eosinophilic gastroenteritis. *J Natl Med Assoc* 2006; **98**: 1616-1619 [PMID: 17052051]
- 8 Baek MS, Mok YM, Han WC, Kim YS. A patient with eosinophilic gastroenteritis presenting with acute pancreatitis and ascites. *Gut Liver* 2014; **8**: 224-227 [PMID: 24672666 DOI: 10.5009/gnl.2014.8.2.224]
- 9 Elliott JA, McCormack O, Tchrakian N, Conlon N, Ryan CE, Lim KT, Ullah N, Mahmud N, Ravi N, McKiernan S, Feighery C, Reynolds JV. Eosinophilic ascites with marked peripheral eosinophilia: a diagnostic challenge. *Eur J Gastroenterol Hepatol* 2014; **26**: 478-484 [PMID: 24535594 DOI: 10.1097/MEG.0000000000000037]
- 10 Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990; **31**: 54-58 [PMID: 2318432 DOI: 10.1136/gut.31.1.54]
- 11 Zheng X, Cheng J, Pan K, Yang K, Wang H, Wu E. Eosinophilic enteritis: CT features. *Abdom Imaging* 2008; **33**: 191-195 [PMID: 17387538 DOI: 10.1007/s00261-007-9209-1]
- 12 Salgueiro P, Magalhães R, Lago P. Cramping pain and eosinophilic ascites: what is the diagnosis? *Gastroenterology* 2013; **144**: 1353, 1577 [PMID: 23623877 DOI: 10.1053/j.gastro.2013.01.008]
- 13 Zhang L, Duan L, Ding S, Lu J, Jin Z, Cui R, McNutt M, Wang A. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. *Scand J Gastroenterol* 2011; **46**: 1074-1080 [PMID: 21623674 DOI: 10.3109/00365521.2011.579998]
- 14 Pineton de Chambrun G, Desreumaux P, Cortot A. Eosinophilic enteritis. *Dig Dis* 2015; **33**: 183-189 [PMID: 25925921 DOI: 10.1159/000369540]
- 15 Casella G, Villanacci V, Bassotti G. Eosinophilic ascites resolution with ketotifen. *Mayo Clin Proc* 2011; **86**: 1027 [PMID: 21964180 DOI: 10.4065/mcp.2011.0408]

P- Reviewer: Losanoff JE, Ooi LLPJ, Pani SP, Xavier-Elsas P

S- Editor: Ji FF L- Editor: A E- Editor: Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

