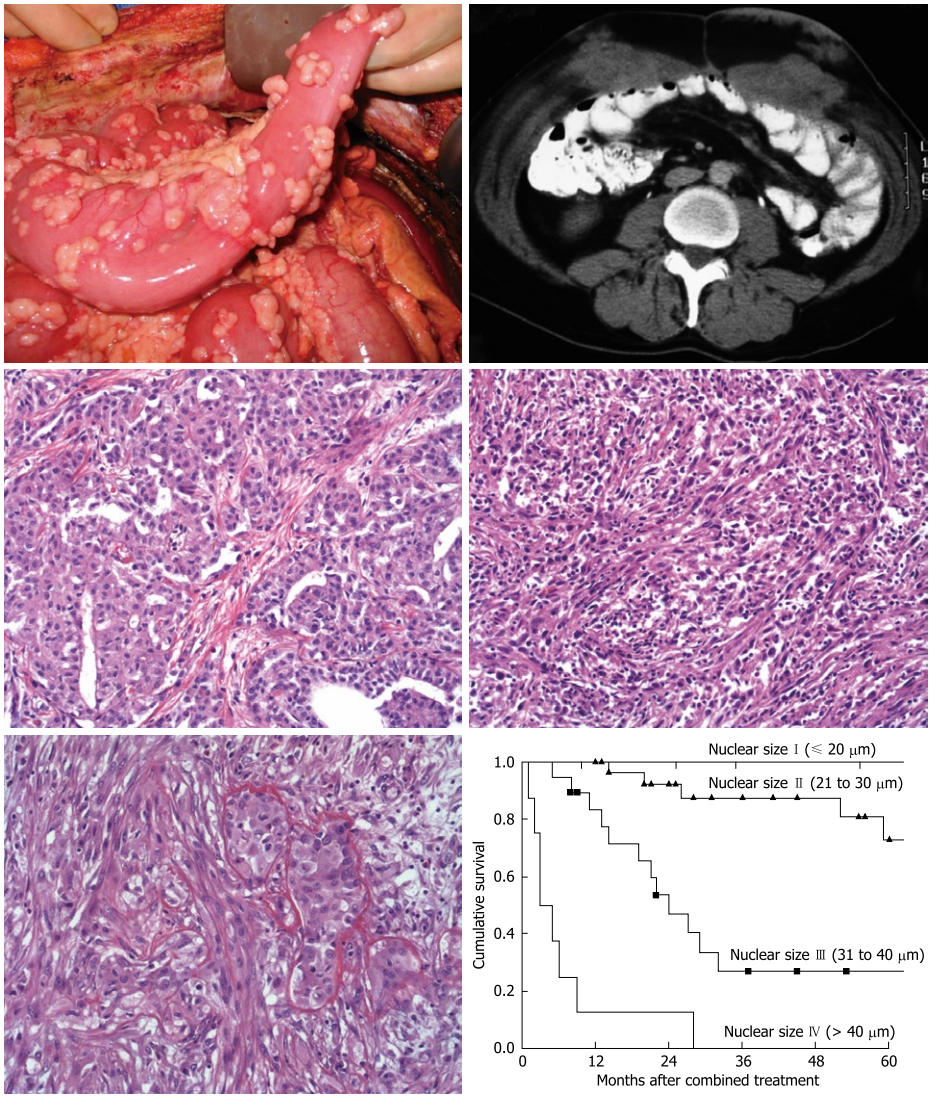
ISSN 1948-9366 (online)

WJGS

World Journal of Gastrointestinal Surgery

World J Gastrointest Surg 2009 November 30; 1(1): 1-70

A peer-reviewed, online, open-access journal of gastrointestinal surgery



WJGS World Journal of Gastrointestinal Surgery

A peer-reviewed, online, open-access journal of gastrointestinal surgery

Editorial Board

2009-2013

The *World Journal of Gastrointestinal Surgery* Editorial Board consists of 328 members, representing a team of worldwide experts in surgery research. They are from 35 countries, including Australia (6), Austria (2), Belgium (5), Brazil (9), Bulgaria (2), Canada (8), China (30), Denmark (1), Finland (1), France (10), Germany (21), Greece (6), India (9), Ireland (3), Israel (3), Italy (49), Jamaica (1), Japan (44), Malaysia (1), Pakistan (1), Poland (1), Portugal (1), Russia (1), Singapore (5), Serbia (1), South Korea (9), Spain (3), Sweden (1), Switzerland (4), Thailand (2), The Netherlands (9), Tunisia (1), Turkey (8), United Kingdom (7), and United State (62).

France

Chapel Alain, *Far*
Mustapha Adham, *Lyon*
Brice Gayet, *Paris*
Jean-François Gillion, *Antony*
D Heresbach, *Rennes Cedex*
Romaric Loffroy, *Dijon Cedex*
Jacques Marescaux, *Strasbourg Cedex*
Yves Panis, *Clichy*
Aurélie Plessier, *Clichy*
Eric Savier, *Paris*

Germany

Vollmar Brigitte, *Rostock*
Dieter C Broering, *Kiel*
Hans G Beger, *Ulm*
Ansgar M Chromik, *Bochum*
Marc-H Dahlke, *Regensburg*
Irene Esposito, *Neuherberg*
Stefan Fichtner-Feigl, *Regensburg*
Benedikt Josef Folz, *Bad Lippspringe*
Helmut Friess, *München*
Reinhart T Grundmann, *Burghausen*
Bertram Illert, *Würzburg*
Jakob R Izbicki, *Hamburg*
Haier Jörg, *Münster*
Jörg H Kleeff, *Munich*
Uwe Klinge, *Aachen*
Martin G Mack, *Frankfurt*
Klaus Erik Mönkemüller, *Bottrop*
Matthias Peiper, *Moorenstrasse*
Hubert Scheidbach, *Magdeburg*
Joerg Theisen, *Munich*

Greece

Eelco de Bree, *Herakleion*
Stavros J Gourgiotis, *Athens*
Andreas Manouras, *Athens*
Theodoros E Pavlidis, *Thessaloniki*
George H Sakorafas, *Athens*
Vassilios E Smyrniotis, *Athens*

India

Shams-ul-Bari, *Kashmir*
Somprakas Basu, *Varanasi*
Pravin J Gupta, *Nagpur*
Vinay Kumar Kapoor, *Lucknow*
Anil K Agarwal MCh, *New Delhi*
Chandra Kant Pandey, *Lucknow*
Shailesh V Shrikhande, *Mumbai*
Sadiq S Sikora, *Bangalore*
Prod Rakesh K Tandon, *New Delhi*

Ireland

Kevin C P Conlon, *Dublin*
Prem Puri, *Dublin*
Eamonn M Quigley, *Cork*

Israel

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

Italy

Angelo Andriulli, *San Giovanni Rotondo*
Giuseppe Aprile, *Udine*
Gianni Biancofiore, *Pisa*
Stefania Boccia, *Rome*
Luigi Bonavina, *San Donato*
Pier Andrea Borea, *Ferrara*
Giovanni Cesana, *Milan*
Stefano Crippa, *Verona*
Giovanni D De Palma, *Napoli*
Giovanni De Simone, *Napoli*
Francesco Di Costanzo, *Perugia*
Giuseppe Malleo, *Verona*
Giorgio Ercolani, *Bologna*
CarloV Feo, *Ferrara*
Simone Ferrero, *Genova*
Valenza Franco, *Milano*
Leandro Gennari, *Milan*
Felice Giuliante, *Roma*
Salvatore Gruttadauria, *Palermo*
Calogero Iacono, *Verona*
Riccardo Lencioni, *Pisa*
Dottor Fabrizio Luca, *Milan*
Paolo Massucco, *Candiolo*
Giorgio Di Matteo, *Roma*
Giulio Melloni, *Milan*
Manuela Merli, *Roma*
Paolo Morgagni, *Forlì*
Chiara Mussi, *Rozzano*
Gabriella Nesi, *Florence*
Angelo Nespoli, *Monza*
Fabio Pacelli, *Rome*
Corrado Pedrazzani, *Siena*
Roberto Persiani, *Rome*
Piero Portincasa, *Bari*
Pasquale Petronella, *Napoli*
Stefano Rausei, *Varese*
Carla Ida Ripamonti, *Milan*
Antonio Russo, *Palermo*
Giulio A Santoro, *Treviso*
Stefano Scabini, *Genoa*
Gianfranco Silecchia, *Roma*
Guido AM Tiberio, *Roma*
Umberto Veronesi, *Milano*
Bruno Vincenzi, *Rome*
Marco Vivarelli, *Bologna*
Alberto Zaniboni, *Brescia*
Alessandro Zerbi, *Milan*

Jamaica

Joseph M Plummer, *Kingston*

Japan

Yasunori Akutsu, *Chiba*
Ryuichiro Doi, *Kyoto*
Yosuke Fukunaga, *Sakai*
Akira Furukawa, *Shiga*
Kazuhiko Hayashi, *Tokyo*
Naoki Hiki, *Tokyo*
Tsujimoto Hironori, *Tokorozawa*
Tsukasa Hotta, *Wakayama*
Kazuaki Inoue, *Yokohama*
Masashi Ishikawa, *Tokushima*
Tatsuo Kanda, *Niigata*
Tatsuyuki Kawano, *Tokyo*
Keiji Koda, *Chiba*
Hajime Kubo, *Kyoto*
Iruru Maetani, *Tokyo*
Yoshimasa Maniwa, *Kobe*
Toru Mizuguchi, *Hokkaido*
Zenichi Morise, *Toyoake*
Yoshihiro Moriwaki, *Yokohama*
Yoshihiro Moriya, *Tokyo*
Satoru Motoyama, *Akita*
Hiroaki Nagano, *Osaka*
Masato Nagino, *Nagoya*
Toshio Nakagohri, *Kashiwa*
Kazuyuki Nakamura, *Yamaguchi*
Shingo Noura, *Osaka*
Kazuo Ohashi, *Tokyo*
Yoichi Sakurai, *Toyoake*
Hirozumi Sawai, *Nagoya*
Masayuki Sho, *Nara*
Yasuhiko Sugawara, *Tokyo*
Hiroshi Takamori, *Kumamoto*
Sonshin Takao, *Kagoshima*
Hiromitsu Takeyama, *Nagoya*
Kuniya Tanaka, *Yokohama*
Masanori Tokunaga, *Shizuoka*
Akira Tsunoda, *Chiba*
Toshifumi Wakai, *Niigata*
Jiro Watari, *Nishinomiya*
Shinichi Yachida, *Kagawa*
Yasushi Yamauchi, *Fukuoka*
Hiroki Yamaue, *Wakayama*
Yutaka Yonemura, *Osaka*

Malaysia

Way Seah LEE, *Lumpur*

Pakistan

Kamran Khalid, *Lahore*

Poland

Bogusław Machaliński, *Szczecin*

Portugal

Jorge Correia-Pinto, *Braga*

Russia

Grigory G Karmazanovsky, *Moscow*

Singapore

Salleh bin Ibrahim, *Singapore*

John M Luk, *Singapore*
Francis Seow-Choen, *Elizabeth*
Vishalkumar G Shelat, *Singapore*
Melissa Teo, *Singapore*

Serbia

Ivan Jovanovic, *Belgrade*

South Korea

Joon Koo Han, *Seoul*
Hyung-Ho Kim, *Seongnam*
Woo Ho Kim, *Seoul*
Sang Y Lee, *Gyeongsangnam-do*
Woo Yong Lee, *Seoul*
Hyo K Lim, *Seoul*
Jae-Hyung Noh, *Seoul*
Sung Hoon Noh, *Seoul*
Hee Jung Wang, *Suwon*

Spain

Antonio M Lacy Fortuny, *Barcelona*
Laura L Garriga, *Barcelona*
Francisco José Vizoso, *Gijón*
David Parés, *Barcelona*

Sweden

Jörgen Rutegård, *Umeå*

Switzerland

Andrea Frilling, *Zürich*
Pascal Gervaz, *Genève*
Bucher Pascal, *Geneva*
Marc Pusztaszeri, *Carouge*

Thailand

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

The Netherlands

Lee H Bouwman, *Hague*
Wim A Buuman, *Maastricht*
Robert Chamuleau, *Amsterdam*
Miguel A Cuesta, *Amsterdam*
Jeroen Heemskerk, *Roermond*
Buis Carlijn Ineke, *Deventer*
Wjhj Meijerink, *Amsterdam*
Chj van Eijck, *Rotterdam*
Alexander L Vahrmeijer, *Leiden*

Tunisia

Nafaa Arfa, *Tunis*

Turkey

Ziya Anadol, *Ankara*
Unal Aydin, *Gaziantep*
Mehmet Fatih Can, *Ankara*
Gözde Kir, *Istanbul*
Adnan Narci, *Afyonkarahisar*
Ilgin Ozden, *İstanbul*
Mesut Abdulkerim Ünsal, *Istanbul*
Omer Yoldas, *Ordu*

United Kingdom

Graeme Alexander, *Cambridge*
Simon R Bramhall, *Birmingham*
Giuseppe Fusai, *London*
Najib Haboubi, *Manchester*
Gianpiero Gravante, *Leicester*
Aftab Alam Khan, *Kent*
Caroline S Verbeke, *Leeds*

United States

Eddie K Abdalla, *Houston*
Forse Robert Armour, *Omaha*
Samik K Bandyopadhyay, *Kolkata*
Marc D Basson, *Lansing*
James M Becker, *Boston*
Thomas D Boyer, *Tucson*
Michael E de Vera, *Pittsburgh*
Andrew J Duffy, *New Haven*
Kelli Bullard Dunn, *Buffalo*
Thomas Fabian, *New Haven*
P Marco Fisichella, *Maywood*
Raja M Flores, *New York*
Markus Frank, *Boston*
Niraj J Gusani, *Hershey*
Douglas W Hanto, *Boston*
John P Hoffman, *Philadelphia*
Scott A Hundahl, *California*
Michel Kahaleh, *Charlottesville*
David S Kauvar, *San Antonio*
Mary M Kemeny, *New York*
Nancy E Kemeny, *New York*
Vijay P Khatri, *Sacramento*
Joseph Kim, *Duarte*
Andrew Klein, *Los Angeles*
Richard A Kozarek, *Seattle*
Robert A Kozol, *Farmington*
Sunil Krishnan, *Houston*
Atul Kumar, *New York*
Wei Li, *Seattle*
Keith D Lillemoe, *Indianapolis*
Henry T Lynch, *Omaha*
Paul Ellis Marik, *Philadelphia*
Robert C Miller, *Rochester*
Thomas J Miner, *Providence*
Ravi Murthy, *Houston*
Atsunori Nakao, *Pittsburgh*
Hirofumi Noguchi, *Dallas*
Jeffrey A Norton, *Stanford*
Timothy M Pawlik, *Baltimore*
Nicholas J Petrelli, *Newark*
Alessio Pigazzi, *Duarte*
James John Pomposelli, *Carlisle*
Mitchell C Posner, *Chicago*
Alexander S Rosemurgy, *Florida*
Ng Chaan S, *Houston*
Sukamal Saha, *Flint*
Reza F Saidi, *Boston*
Aaron R Sasson, *Omaha*
Christian M Schmidt, *Indianapolis*
Perry Shen, *Winston-Salem*
Ali A Siddiqui, *Dallas*
Frank A Sinicrope, *Rochester*
Thomas Earl Starzl, *Pittsburgh*
John H Stewart, *Winston-Salem*
Paul H Sugarbaker, *Washington*
Douglas S Tyler, *Durham*
Vic Velanovich, *Detroit*
Alan Wilkinson, *Los Angeles*
M Michael Wolfe, *Boston*
Christopher L Wolfgang, *Baltimore*
Youmin Wu, *Little Rock*
Zhi Zhong, *Charleston*

WJGS

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 1 Number 1 November 30, 2009

World Journal of Gastrointestinal Surgery
Volume 1 **Number** 1 **November** 30, 2009

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

LAUNCH DATE
November 30, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Gastrointestinal Surgery*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +0086-10-8538-1891
Fax: +0086-10-8538-1893
E-mail: wjgs@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
November 30, 2009

CSSN
ISSN 1948-9366 (online)

EDITORIAL OFFICE
Lai-Fu Li, Director
World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1891
Fax: 0086-10-8538-1893
E-mail: wjgs@wjgnet.com
http://www.wjgnet.com

SPECIAL STATEMENT
All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-9366/index.htm. If you do not have web access please contact the editorial office.

ONLINE SUBMISSION
http://www.wjgnet.com/1948-9366office

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.1

World J Gastrointest Surg 2009 November 30; 1(1): 1-2
ISSN 1948-9366 (online)

EDITORIAL

What is the purpose of launching *World Journal of Gastrointestinal Surgery*?

Lian-Sheng Ma

Lian-Sheng Ma, Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Author contributions: Ma LS solely contributed to this paper.
Correspondence to: Lian-Sheng Ma, Professor, President and Editor-in-Chief, Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China. l.s.ma@wjgnet.com
Telephone: +86-10-59080036 Fax: +86-10-85381893
Received: July 21, 2009 Revised: August 13, 2009
Accepted: August 20, 2009
Published online: November 30, 2009

Abstract

The first issue of *World Journal of Gastrointestinal Surgery* (*WJGS*), whose preparatory work was initiated on September 27, 2008, will be published on November 30, 2009. The *WJGS* Editorial Board has now been established and consists of 328 distinguished experts from 35 countries. Our purpose of launching *WJGS* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

Key words: Maximization of personal benefits; Editorial board members; Authors; Readers; Employees; *World Journal of Gastrointestinal Surgery*

Ma LS. What is the purpose of launching *World Journal of Gastrointestinal Surgery*? *World J Gastrointest Surg* 2009; 1(1): 1-2 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/1.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.1

INTRODUCTION

I am very pleased to announce that the first issue of *World Journal of Gastrointestinal Surgery* (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) will be published on November 30, 2009, whose preparatory work was initiated on September 27, 2008. The *WJGS* Editorial Board has now been established and consists of 328 distinguished experts from 35 countries.

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. To realize these desired attributes of a journal and create a well-recognized journal, the following four types of personal benefits should be maximized.

MAXIMIZATION OF PERSONAL BENEFITS

The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others.

Maximization of the benefits of editorial board members

The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in

that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution.

Maximization of the benefits of authors

Since *WJGS* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGS* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading.

Maximization of the benefits of readers

Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion[1].

Maximization of the benefits of employees

It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal[2,3]. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJGS* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

SCOPE

The major task of *WJGS* is to report rapidly the most recent results in basic and clinical research on gastrointestinal surgery, including: micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects, such as: epidemiology, cancer research, biomarkers, prevention, pathology, radiology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, molecular biology, clinical trials, diagnosis and therapeutics and multimodality treatment. This journal will also provide balanced, extensive and timely review articles on selected topics.

COLUMNS

The columns in *WJGS* will include: (1) Editorial: to introduce and comment on major advances in rapidly developing areas and their importance; (2) Frontier: to review recent developments, comment on current research status in important fields, and propose directions for future research; (3) Topic Highlight: this column consists of three formats, including: (a) 10 invited review articles on a hot topic; (b) a commentary on common issues associated with this hot topic; and (c) a commentary on the 10 individual articles; (4) Observation: to update the development of old and new questions, highlight unsolved problems, and provide strategies for their resolution; (5) Guidelines for Basic Research: to provide guidelines for basic research; (6) Guidelines for Clinical Practice: to provide guidelines for clinical diagnosis and treatment; (7) Review: to review systemically the most representative progress and unsolved problems, comment on current research status, and make suggestions for future work; (8) Original Article: to report original and innovative findings; (9) Brief Article: to report briefly on novel and innovative findings; (10) Case Report: to report a rare or typical case; (11) Letters to the Editor: to discuss and reply to contributions published in *WJGS*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: to introduce and comment on quality monographs; and (13) Guidelines: to introduce consensuses and guidelines reached by international and national academic authorities on basic research and clinical practice.

REFERENCES

1 **Zhu DM**. What is the purpose of literature citation? Science Times, 2009-07-17. Available from: URL: http://www.sciencenet.cn/htmlnews/2009/7/221552.shtm
2 **Li ZX**. See the "sallying forth" of Chinese scientific and technical journals from the innovative business model of *WJG*. *Zhongguo Keji Qikan Yanjiu* 2008; **19**: 667-671
3 **Xiao H**. First-class publications can not do without first-class editorial talents. *Keji Yu Chuban* 2008; **3**: 192

S- Editor Li LF **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.3

World J Gastrointest Surg 2009 November 30; 1(1): 3-5
ISSN 1948-9366 (online)

EDITORIAL

Glycemic control in critically ill patients: What to do post NICE-SUGAR?

Paul E Marik

Paul E Marik, Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, VA 23507, United States
Author contributions: Marik PE contributed solely to this editorial.
Correspondence to: Paul E Marik, MD, FCCP, FCCM, Professor of Medicine, Chief of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, VA 23507, United States. marikpe@evms.edu
Telephone: +1-757-4468910 Fax: +1-757-4465242
Received: July 2, 2009 Revised: November 9, 2009
Accepted: November 16, 2009
Published online: November 30, 2009

Abstract

Until recently, stress hyperglycemia was considered to be a beneficial adaptive response, with raised blood glucose providing a ready source of fuel for the brain, skeletal muscle, heart and other vital organs at a time of increased metabolic demand. Following the Leuven Intensive Insulin Therapy Trial in 2001, tight glycemic control became rapidly adopted as the standard of care in intensive care units (ICU's) throughout the world. However, four randomized controlled studies and the recently published NICE-SUGAR study have subsequently been unable to replicate the findings of the Leuven Intensive Insulin Therapy Trial. This paper offers an explanation for these discordant findings, and provides a practical approach to glucose control in the ICU.

Key words: Stress hyperglycemia; Intensive care; Critical care; Glucose; Insulin

Peer reviewer: José Eduardo Aguilar Nascimento, MD, Department of Surgery Julio Muller University Hospital Rua Estevao de Mendonca 81 apto 801, Cuiaba, MT78043-300, Brazil

Marik PE. Glycemic control in critically ill patients: What to do post NICE-SUGAR? *World J Gastrointest Surg* 2009; 1(1): 3-5 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/3.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.3

INTRODUCTION

Stress hyperglycemia is common in critically ill and injured patients and is a component of the "fight or flight" response. Excessive counter regulatory hormones, such as glucagon, growth hormone, catecholamines, and glucocorticoids, as well as cytokines, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α), result in increased gluconeogenesis and insulin resistance, which are the major factors leading to stress hyperglycemia. Until recently, stress hyperglycemia was considered to be a beneficial adaptive response, with raised blood glucose providing a ready source of fuel for the brain, skeletal muscle, heart and other vital organs at a time of increased metabolic demand. However, retrospective studies in patients undergoing cardiac surgery have suggested that peri-operative hyperglycemia was associated with an increased risk of post-operative infections and increased mortality[1-3]. Furthermore, these studies suggested that control of blood glucose reduced these complications. Hyperglycemia increases oxidative injury, potentiates the pro-inflammatory response, promotes clotting, causes abnormal vascular reactivity and impairs leukocyte and mononuclear cell immune responsiveness[4,5].

GLYCEMIC CONTROL IN THE INTENSIVE CARE UNIT (ICU)

In 2001, van den Berghe and coworkers published a "landmark study" (the Leuven Intensive Insulin Therapy Trial) in which they demonstrated that tight glycemic control (blood glucose between 80-110 mg/dL) using

intensive insulin therapy improved the outcome of critically ill surgical patients[6]. Following this study, tight glycemic control was rapidly adopted as the standard of care in ICUs throughout the world and was endorsed by the Institute for Health Care Improvement and other national organizations in the USA and abroad. In 2006, van den Berghe and colleagues repeated the study design in medical ICU patients[7]. Although failing to reproduce improvement in survival in the entire set of patients, this study demonstrated a reduction in morbidity in the patients randomized to the tight glycemic group with a reduction in mortality in the subset of patients with an ICU stay of three days or more. Following this study, two multicenter, randomized European studies were prematurely discontinued due to an alarmingly high rate of hypoglycemia in the "tight glycemic control" arm with no mortality benefit[8,9]. Two additional single center, randomized studies showed a trend towards a higher mortality in the in the "tight glycemic control" arm[10,11]. Recently, a large (6022 patients) multicenter, randomized controlled study (the NICE-SUGAR study[12]), was published that was unable to confirm the findings of van den Berghe *et al*[6,7]. Indeed, this study demonstrated a 2.6% absolute increase in 90-d mortality in patients randomized to tight glucose control (P = 0.02). Summary data of these five studies (excluding the van den Berghe *et al*[6,7] studies) demonstrated that intensive insulin therapy is associated with an increased risk of death with mortality being significantly lower in the control group (OR 0.89; 95% CI 0.81-0.99, P = 0.04).

The explanation for the disparate findings between the van den Berghe *et al*[6,7] studies and subsequent studies probably lies with the high rate of use of parenteral nutrition (TPN) in the van den Berghe *et al*[6,7] studies. In both van den Berghe *et al*[6,7] studies, 87% of the calories were provided *via* the intravenous route[13]. TPN is associated with severe hyperglycemia. It would therefore appear counter intuitive to administer large amount of intravenous glucose to patients with stress hyperglycemia; this will only compound the degree of hyperglycemia. Van der Voort and colleagues have demonstrated that the ICU and hospital mortality of critically ill patients was independently related to the mean amount of infused glucose[14]. In a retrospective analysis of 111 hospitalized patients receiving TPN, Cheung and coworkers reported that hyperglycemia was independently associated with an increased risk of cardiac complications, sepsis, acute renal failure and death[15]. In this study, the mortality of subjects with blood glucose in the highest quartile was 10.9 times that of subjects in the lowest quartile. These data suggest that TPN may have increased mortality in the control arm of the van den Berghe *et al*[13] studies; and this may have accounted for the apparent benefit from tight glycemic control in those treated with insulin to achieve a blood glucose of between 80-110 mg/dL. Indeed, a mortality of 8% (control arm) in predominantly elective cardiac surgery patients (with a median APACHE Ⅱ score of 9), appears rather high.

Tight glycemic control in ICU patients is not benign and this may account for the higher mortality in the intensive insulin group in the NICE-SUGAR study. The "harm" of tight glycemic control may be due to the high rate of both absolute (blood glucose < 40 mg/dL) and relative hypoglycemia (blood glucose 40-80 mg/dL) in these patients[7]. Glucose is the sole source of energy for the brain with demand increasing during stress. Using cerebral microdialysis in patients following severe brain injury, Oddo and colleagues demonstrated that tight glycemic control is associated with a greater risk of brain energy crisis and death[16]. It would therefore appear that in critically ill patients, hyperglycemia (especially that induced by TPN) is not desired, but that "low" blood glucose is even less desired.

The results of the NICE-SUGAR study, as well as the additional four randomized controlled studies that have attempted to replicate the van den Berghe *et al*[6,7] studies, clearly demonstrate that tight glycemic control (70-110 mg/dL) has a limited role in the management of general ICU patients. However, the role of tight glycemic control in patients undergoing cardiac surgery remains unclear. In these patients, it is likely that both pre- and post-operative optimization of blood glucose may improve outcome, however, the optimal blood glucose target is unknown (probably between 100-140 mg/dL). In all other ICU patients, it appears reasonable to maintain the blood glucose concentration between 140-200 mg/dL. The optimal method for achieving this goal is unclear, however, a number of options are available. In the control arm of the NICE-SUGAR study, an insulin infusion was administered if the blood glucose level exceeded 180 mg/dL, insulin administration was subsequently reduced and then discontinued if the blood glucose level dropped below 144 mg/dL. In our practice, we avoid parenteral nutrition as there is no data suggesting this mode of nutritional support has any advantages over enteral nutrition[17,18]. Furthermore, we use an enteral formula with a high concentration of lipids (omega-3 fatty acids) and we avoided overfeeding[19]. Mesejo and colleagues demonstrated that ICU patients fed a "diabetic" tube feed had better glucose control than those fed a standard enteral formula[20]. In those patients whose blood glucose remained greater than 180 mg/dL, we used a twice daily regimen of intermediate acting insulin together with insulin amounts on a sliding scale to keep the blood glucose less than 180 mg/dL. We limited the NPH-intermediate insulin to a maximum of 20 units in 12 h. If this approach did not adequately control blood glucose (< 200 mg/dL), we then switched to an insulin infusion. Although the use of sliding scales for insulin administration in hospitalized patients (who are eating) is considered a"relic from the past" (and reactive rather than proactive) this approach does have some utility in ICU patients who are receiving continuous tube feeds[21]. Further, although the absorption of subcutaneous insulin may be impaired in the critically ill, absorption may be adequate for the control of blood glucose.

REFERENCES

1 **Furnary AP**, Wu Y. Clinical effects of hyperglycemia in the cardiac surgery population: the Portland Diabetic Project. *Endocr Pract* 2006; **12** Suppl 3: 22-26
2 **Furnary AP**, Wu Y. Eliminating the diabetic disadvantage: the Portland Diabetic Project. *Semin Thorac Cardiovasc Surg* 2006; **18**: 302-308
3 **Zerr KJ**, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg* 1997; **63**: 356-361
4 **McCowen KC**, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001; **17**: 107-124
5 **Marik PE**, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. *Intensive Care Med* 2004; **30**: 748-756
6 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367
7 **van den Berghe G**, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**: 449-461
8 **Devos P**, Preiser JC, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemmia: final results of the Glucontrol study [European society of Intensive Care Medicine 20th Annual Congress abstract 0735]. *Intensive Care Med* 2007; **33** Suppl 2: S189
9 **Brunkhorst FM**, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-139
10 **De La Rosa Gdel C**, Donado JH, Restrepo AH, Quintero AM, González LG, Saldarriaga NE, Bedoya M, Toro JM, Velásquez JB, Valencia JC, Arango CM, Aleman PH, Vasquez EM, Chavarriaga JC, Yepes A, Pulido W, Cadavid CA. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care* 2008; **12**: R120
11 **Arabi YM**, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008; **36**: 3190-3197
12 **Finfer S**, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-1297
13 **van den Berghe G**, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006; **55**: 3151-3159
14 **der Voort PH**, Feenstra RA, Bakker AJ, Heide L, Boerma EC, van der Horst IC. Intravenous glucose intake independently related to intensive care unit and hospital mortality: an argument for glucose toxicity in critically ill patients. *Clin Endocrinol* (Oxf) 2006; **64**: 141-145
15 **Cheung NW**, Napier B, Zaccaria C, Fletcher JP. Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. *Diabetes Care* 2005; **28**: 2367-2371
16 **Oddo M**, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapkovich ND, Levine JM, Le Roux P, Mayer SA. Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. *Crit Care Med* 2008; **36**: 3233-3238
17 **Marik PE**, Pinsky M. Death by parenteral nutrition. *Intensive Care Med* 2003; **29**: 867-869
18 **Elke G**, Schädler D, Engel C, Bogatsch H, Frerichs I, Ragaller M, Scholz J, Brunkhorst FM, Löffler M, Reinhart K, Weiler N. Current practice in nutritional support and its association with mortality in septic patients--results from a national, prospective, multicenter study. *Crit Care Med* 2008; **36**: 1762-1767
19 **Marik PE**, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. *Intensive Care Med* 2008; **34**: 1980-1990
20 **Mesejo A**, Acosta JA, Ortega C, Vila J, Fernández M, Ferreres J, Sanchis JC, López F. Comparison of a high-protein disease-specific enteral formula with a high-protein enteral formula in hyperglycemic critically ill patients. *Clin Nutr* 2003; **22**: 295-305
21 **Umpierrez GE**, Palacio A, Smiley D. Sliding scale insulin use: myth or insanity? *Am J Med* 2007; **120**: 563-567

S- Editor Li LF **L- Editor** Lutze M **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.6

World J Gastrointest Surg 2009 November 30; 1(1): 6-7
ISSN 1948-9366 (online)

EDITORIAL

Liver regeneration, stem cells and beyond

Marcelo AF Ribeiro Jr

Marcelo AF Ribeiro Jr, Department of Surgery, Santo Amaro University, Alameda Gregorio Bogossian Sobrinho, 80/155, Santana de Parnaiba - SP, 06543-385, Brazil
Author contributions: Ribeiro Jr MAF contributed solely to this editorial.
Correspondence to: Marcelo AF Ribeiro Jr, MD, PhD, FACS, Professor, Department of Surgery, Santo Amaro University, Alameda Gregorio Bogossian Sobrinho, 80/155, Santana de Parnaiba - SP, 06543-385, Brazil. mribeiro@cwaynet.com.br
Telephone: +55-11-38455820 Fax: +55-11-38495271
Received: November 6, 2009 Revised: November 10, 2009
Accepted: November 17, 2009
Published online: November 30, 2009

Abstract

Studies of the liver regenerative process have gained prominence in the last few years, especially with the interest in stem cell therapy. The regenerative capacity of the liver, its mechanisms and the role of stem cells will be discussed in this editorial as well as the role of artificial tissues and organs aiming to produce a new liver based on the current literature.

Key words: Liver; Regeneration; Stem cells; Transplant

Peer reviewer: Uwe Klinge, MD, Professor, Surgical Department of the University Hospital, RWTH Aachen Pauwelsstraße 30 52074 Aachen, Germany

Ribeiro Jr MAF. Liver regeneration, stem cells and beyond. *World J Gastrointest Surg* 2009; 1(1): 6-7 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/6.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.6

INTRODUCTION

Studies of the liver regenerative process have gained prominence in the last few years, especially with the interest in stem cell therapy. The demand for whole liver transplantation in humans far outweighs the organ supply. There is sometimes confusion and often misinterpretation among the liver community regarding the cellular mechanisms responsible for liver regeneration in different types of hepatic growth processes. From the clinical point of view, transplantation of hepatocytes or hepatocyte-like cells could represent an alternative either to orthotopic liver transplant in acute liver failure or for the correction of genetic disorders resulting in metabolically deficient states.

STATE OF THE ART

The source of hepatocytes during regeneration will depend on the nature of the growth process. As pointed out by Fausto[1], in every case it is necessary to ascertain whether it has originated from replication of existing hepatocytes, was generated by differentiation of oval cells or was produced from bone marrow cells. Replication of existing hepatocytes is the quickest and most effective way to generate hepatocytes for liver regeneration and repair.

It is well establish that oval cells will only replicate and differentiate into hepatocytes when the mature hepatocyte replication is delayed or entirely blocked. It is also known that bone marrow cells can generate hepatocytes in transplanted livers but often the frequency of hepatocytes produced by this route is very low. Bone marrow cells play a role as an important source of nonparenchymal cells such as Kupffer cells and endothelial cells.

When considering the origin of intrahepatic bile ducts in liver development and the oval cells in adult liver Endodermal-derived hepatoblasts originate both hepatocytes and intrahepatic bile ducts that express albumin and α-fetoprotein (AFP)[2,3]. At the present, it is established that a bipotential hepatic progenitor cell (HPC) population expands in human liver diseases. Together with indigenous hepatic stem cells, stem cells within the bone marrow are also activated during liver disease and play central roles in inflammation and tissue remodeling. Somatic stem cells are expected to display certain characteristics: (1) self-renewal, (2) multipotentiality, (3) transplantability and (4) functional

long-term tissue reconstitution. Stem cells themselves are required to maintain their undifferentiated state while dividing. Progenitor cells in contrast show a limited ability to self-renew. They comprise distinct subpopulations with variable lineage potential. Moreover unlike stem cells, progenitor cells divide rapidly but cannot be serially transplanted and hence have been named transit amplifying cells. Activation in the context of stem cells refers to an expansion of cell number by proliferation combined with differentiation towards different lineages. HPCs are thought to be bipotential progenitors capable of forming either hepatocytes or cholangiocytes.

The mechanisms controlling the HPC response are under intense investigation. Acute liver injury does not significantly activate the HPC compartment. The most common context in which the HPC reaction is seen is when the cell cycle in hepatocyte regeneration is blocked either by toxins or replicative senescence in rodent models or human diseases. Members of the pro-inflammatory tumour necrosis factor (TNF) superfamily include TNF-α and TWEAK (TNF-like weak induction of apoptosis), both of which appear to play pivotal roles in HPC activation. TNF-α and lymphotoxin (LT), play important roles in both HPC and hepatocyte-mediated regeneration, TWEAK stands out by demonstrating differential effects on the mature hepatocyte and progenitor cells compartments. This therefore positions TWEAK as arguably the most important intercellular signal for inducing the HPC response[4].

Recently a new research field has been developing, the generation of artificial tissues and organs for clinical use. Their main indications in the clinical settings are as sources of material for transplantation, models to study diseases, drug efficacy, and cellular behavior or phenotype. The creation of an artificial tissue requires an extracellular matrix that has architectural, mechanical, and chemical properties similar to the tissue of interest. The ideal matrix should also be perfusable, and withstand physiological culture conditions such as fluid-flow-induced mechanical stress and strain.

Detergent-based perfusion decellularization of whole cadaveric tissues provides a platform for tissue engineering, since after decellularization a matrix with native chemistry, architecture and mechanical properties is left. This decellularized matrix can be reseeded with single or multiple cell types, allowing for the isolation and study of matrix effects on cell phenotype from the confounding complexity of normal tissue. This matrix generation has been successfully applied to the recellularization of liver-decellularized matrix using rat or human cells generating functional tissue. Matrix properties are important, because a cell's niche affects cellular phenotype, including but not limited to migration, axonal guidance, proliferation, and differentiation. This holds true not only for differentiated cells but also for embryonic stem cells and adult tissue-specific stem cells or progenitors. Niche interactions can consist of cell-matrix cues (such as glycosaminoglycans and soluble or matrix-bound proteins) and cell-cell and direct cell-matrix interactions. Examples of niche interactions that influence cell phenotype[5-7] include the observations that hepatocytes exhibit greater phenotypic stability in the presence of extracellular matrix in 2D or 3D cultures, whereas matrix chemistry contributes to hepatic zonation, and that mechanically soft matrix induces quiescence of bone-marrow-derived mesenchymal stem cells.

So, today the development of 3-D functional tissues for drug discovery or therapeutic use, is no longer a dream, several centers have already reached it. The main challenges for the scientist will be the development of a bioartificial liver arising from the matrix associated with the stem cells that can replace the sick liver, is able to maintain its main functions of metabolism, synthesis and even regeneration in order to repair subsequent damage, and that provides good quality of life and also decreases the high rates of mortality that these group of patients unfortunately suffer today all over the world on the liver waiting lists.

REFERENCES

1 **Fausto N**. Liver regeneration and repair: hepatocytes, progenitor cells, and stem cells. *Hepatology* 2004; **39**: 1477-1487
2 **Shiojiri N**. The origin of intrahepatic bile duct cells in the mouse. *J Embryol Exp Morphol* 1984; **79**: 25-39
3 **Lemaigre FP**. Development of the biliary tract. *Mech Dev* 2003; **120**: 81-87
4 **Bird TG**, Lorenzini S, Forbes SJ. Activation of stem cells in hepatic diseases. *Cell Tissue Res* 2008; **331**: 283-300
5 **Ben-Ze'ev A**, Robinson GS, Bucher NL, Farmer SR. Cell-cell and cell-matrix interactions differentially regulate the expression of hepatic and cytoskeletal genes in primary cultures of rat hepatocytes. *Proc Natl Acad Sci USA* 1988; **85**: 2161-2165
6 **Bhandari RN**, Riccalton LA, Lewis AL, Fry JR, Hammond AH, Tendler SJ, Shakesheff KM. Liver tissue engineering: a role for co-culture systems in modifying hepatocyte function and viability. *Tissue Eng* 2001; **7**: 345-357
7 **Chang TT**, Hughes-Fulford M. Monolayer and spheroid culture of human liver hepatocellular carcinoma cell line cells demonstrate distinct global gene expression patterns and functional phenotypes. *Tissue Eng Part A* 2009; **15**: 559-567

S- Editor Li LF **L- Editor** Lalor PF **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.8

World J Gastrointest Surg 2009 November 30; 1(1): 8-10
ISSN 1948-9366 (online)

OBSERVATION

Gastroesophageal reflux disease and the airway-essentials for the surgeon

Vic Velanovich

Vic Velanovich, Division of General Surgery, Henry Ford Hospital, Detroit, MI 48202, United States
Author contributions: Velanovich V contributed solely to this paper.
Correspondence to: Vic Velanovich, MD, Division of General Surgery, K-8, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202, United States. vvelano1@hfhs.org
Telephone: +1-313-9168984 Fax: +1-313-9169920
Received: July 24, 2009 Revised: October 24, 2009
Accepted: November 1, 2009
Published online: November 30, 2009

Abstract

Gastroesophageal reflux disease (GERD) has many protean manifestations. Some of the most vexing have to do with the airway. GERD affects the tracheobronchial tree directly, leading to aspiration pneumonia and asthma, or exacerbating existing pulmonary disease, such as asthma or chronic obstructive pulmonary disease. In addition to the respiratory manifestation of GERD, there are unique pharyngeal and laryngeal manifestations. These include voice hoarseness, throat-clearing, chronic cough, globus, and "post-nasal drip". Linking these symptoms to GERD is challenging and frequently the diagnosis is that of exclusion. Despite proton pump inhibitor therapy being the mainstay of treatment, with anti-reflux surgery being reserved for intractable cases, there is no definitive evidence of the superiority of either.

Key words: Gastroesophageal reflux disease; Laryngopharyngeal reflux; Reflux-induced asthma; Aspiration pneumonia; Chronic obstructive pulmonary disease; Chronic cough; Reflux laryngitis

Peer reviewer: Natale Di Martino, Chief Professor and Director of the 8th, Department of General and Gastrointestinal Surgery, Second University of Naples, 3, Miraglia Square, 80138 Naples, Italy

Velanovich V. Gastroesophageal reflux disease and the airway-essentials for the surgeon. *World J Gastrointest Surg* 2009; 1(1): 8-10 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/8.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.8

INTRODUCTION

Gastroesophageal reflux (GER) is the normal physiologic reflux of gastric contents into the esophagus. Various physiologic mechanisms protect the esophagus from injury, including minimizing reflux itself through the lower esophageal sphincter, reflex peristaltic clearing of the esophagus to minimize the time exposure of the esophagus to the acidic contents, a mucus layer on the esophageal epithelium to act as a barrier to the acidic contents, and alkalinization of the acidic contents with saliva. When one or more of these defense mechanisms breaks down, pathologic reflux occurs, leading to symptoms severe enough to affect quality of life and/or cause pathologic changes in the esophagus such as inflammation, ulceration, stricture, Barrett's esophagus and possible adenocarcinoma. Heartburn and regurgitation are the most common symptoms of gastroesophageal reflux disease (GERD), and are therefore, referred to as the "typical" symptoms of GERD. However, GER can affect the upper aerodigestive tract including the hypopharynx, pharynx, larynx, and tracheobronchial tree. These lead to symptoms involving these structures which are different than the typical symptoms of GERD. These symptoms are referred to as the "atypical" or "extra-esophageal" symptoms of GERD, or when specifically associated with the pharynx or larynx, "laryngopharyngeal reflux disease" (LPRD).

RESPIRATORY MANIFESTATIONS OF GERD

Prevalence and magnitude

Because the respiratory manifestations of GERD are so varied, and because different authors have different definitions of what, in fact, constitute respiratory manifestations, the exact prevalence is hard to determine. The best studied prevalence, however, relates to GERD-induced asthma[1], the effects of GERD on chronic obstructive pulmonary disease (COPD)[2], and aspiration pneumonia[3].

Havemann *et al*[1] have performed a systematic review of the prevalence studies of GERD and asthma. The studies have focused on the association of patients with GERD symptoms also having asthma symptoms, abnormal pH monitoring studies, endoscopically-determined esophagitis, and hiatal hernia. Their meta-analysis found an overall odds ratio (OR) of 2.26 with a 95% confidence interval (CI) of 1.81 to 2.83 for the presence of asthma in GERD patients. Alternatively, when evaluating the presence of GERD symptoms in asthmatic patients, they determined an OR of 5.5 with a 95% CI of 1.9 to 15.8.

Although not a cause of COPD, GERD can affect lung function in these patients. Terada *et al*[2] demonstrated that COPD patients were more than twice as likely to suffer from GERD than normal controls (OR 2.13, 95% CI 0.88-5.25), and those COPD patients who suffer from GERD were more than twice as likely to suffer exacerbations of their COPD in any 6 month period (OR 1.93, 95% CI 1.32-2.84). Lastly, in a study of death related to GERD, Rantanen *et al*[3] found that 41 of the 213 deaths related to GERD in Finland from 1987 to 2000 were due to aspiration pneumonia. Therefore, respiratory complications of GERD may be potentially fatal.

Symptoms

The respiratory symptoms and conditions associated GERD include asthma, chronic cough, chronic bronchitis, pulmonary aspiration complications (lung abscess, bronchiectasis, aspiration pneumonitis), idiopathic pulmonary fibrosis, COPD, and obstructive sleep apnea[4]. However, it should be emphasized that a causal, or even an associative, relationship has not been fully determined and controversy exists for many of these conditions[4].

Pathophysiology

The pathophysiology of respiratory symptoms of GERD has not been fully elucidated. Two basic mechanisms have been proposed[1,4]. These include microaspiration of either/both acidic and nonacidic gastric contents into the airway and nervous system-mediated responses. Specifically, with respect to asthma, vagally-mediated bronchospasm has been proposed as an explanation linking asthma and GERD in the absence of aspiration[4]. For cough, in addition to aspiration, normal or abnormal stimulation of afferent nerves, the stimulation of abnormally sensitive afferent nerves, and the abnormal integration of stimulation within the central nervous system have been proposed[4].

Diagnosis

The diagnosis of GERD-related respiratory manifestations can be difficult and is primarily a diagnosis of exclusion. There are many potential causes of these conditions and establishing the causal relationship to GERD can be vexing. Anecdotally, it seems reasonable to place more credence in the diagnosis if the respiratory symptoms appeared or worsened after the onset of GERD symptoms. However, frequently patients will have respiratory symptoms without the typical symptoms of reflux. Therefore, the use of gastrointestinal, laryngeal, and tracheobronchial endoscopy, esophageal manometry, duel channel 24 h pH monitoring, and impedance manometry have been used to supplement the diagnosis[5].

Medical management

Medical management for GERD-related respiratory symptoms has proven to be disappointing. Many studies have been done using a variety of medical acid suppression therapies with proton-pump inhibitors, H_2-blockers, and promotility agents with mixed results. A systematic review of the data has demonstrated no convincing evidence that medical management improves symptoms[4].

Surgical management

Surgical management has been with antireflux operations, specifically laparoscopic Nissen fundoplication. Most of these reports have been uncontrolled studies in highly selected patients. The only prospective comparative study showed that 74% of patients improved with surgery, while only 9% of medically-treated and 4% of controls improved[6].

LARYNGOPHARYNGEAL REFLUX

Prevalence and magnitude

Because the symptoms related to LPRD are common and non-specific, it is difficult to determine the prevalence and magnitude of this condition. In a study of patients presenting with hoarseness, by Cohen *et al*[7] found that over 50% had "secondary" laryngopharyngeal symptoms and over 50% had diagnoses other than LPRD or GERD.

Symptoms

Symptoms of LPRD include dysphonia (voice hoarseness), globus, chronic throat-clearing, chronic cough, sore throat, paroxysmal laryngospasm, idiopathic subglottic stenosis, and postnasal drip[8,9].

Pathophysiology

LPRD is caused by reflux of gastric contents into the hypopharynx and larynx. Reflux of acidic contents into the upper aerodigestive tract is a rare event, with a total time that the pH < 4 is < 0.01%, compared to 4% in the distal esophagus[8]. In addition, it has become increasingly clear that pepsin, in addition to acid, has a role in LPRD[10]. Therefore, patients may manifests symptoms of reflux without exposure to acid. However, the basic defect in the lower esophageal sphincter appears similar

in patients with GERD, LPRD, and mixed GERD/LPRD symptoms[11].

Diagnosis

As with GERD-related respiratory symptoms, LPRD can be a difficult diagnosis to secure. The signs and symptoms are non-specific and can be attributed to several disease conditions. Usually, a combination of laryngoscopy, esophageal manometry, duel-channel 24 h esophageal pH monitoring and, recently, impedance manometry has been used. Some advocate a trial of proton pump inhibitor therapy as a means of diagnosis[8].

Medical management

Several trials have been conducted evaluating the effectiveness of PPI therapy in relieving the symptoms of LPRD. The results have been mixed. A meta-analysis of the existing trials shows a modest, but not statistically significant, result favoring PPI treatment (OR 2.0, 95% CI 0.84-3.16).

Surgical management

Studies evaluating the effectiveness of surgical fundoplication on LPRD are surprisingly lacking. The only controlled trial available assessed the symptom relief of laparoscopic Nissen fundoplication in patients who were not responsive to PPI therapy. In this group of patients, fundoplication also did not improve symptoms[12]. However, it is unclear how these data relate to patients with LPRD as a whole.

REFERENCES

1 **Havemann BD**, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut* 2007; **56**: 1654-1664

2 **Terada K**, Muro S, Sato S, Ohara T, Haruna A, Marumo S, Kinose D, Ogawa E, Hoshino Y, Niimi A, Terada T, Mishima M. Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. *Thorax* 2008; **63**: 951-955

3 **Rantanen TK**, Sihvo EI, Räsänen JV, Salo JA. Gastroesophageal reflux disease as a cause of death is increasing: analysis of fatal cases after medical and surgical treatment. *Am J Gastroenterol* 2007; **102**: 246-53

4 **Galmiche JP**, Zerbib F, Bruley des Varannes S. Review article: respiratory manifestations of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008; **27**: 449-464

5 **Tokayer AZ**. Gastroesophageal reflux disease and chronic cough. *Lung* 2008; **186** Suppl 1: S29-S34

6 **Sontag SJ**, O'Connell S, Khandelwal S, Greenlee H, Schnell T, Nemchausky B, Chejfec G, Miller T, Seidel J, Sonnenberg A. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. *Am J Gastroenterol* 2003; **98**: 987-999

7 **Cohen SM**, Garrett CG. Hoarseness: is it really laryngopharyngeal reflux? *Laryngoscope* 2008; **118**: 363-366

8 **Mahieu HF**. Review article: The laryngological manifestations of reflux disease; why the scepticism? *Aliment Pharmacol Ther* 2007; **26** Suppl 2: 17-24

9 **Vaezi MF**. Laryngeal manifestations of gastroesophageal reflux disease. *Curr Gastroenterol Rep* 2008; **10**: 271-277

10 **Mims JW**. The impact of extra-esophageal reflux upon diseases of the upper respiratory tract. *Curr Opin Otolaryngol Head Neck Surg* 2008; **16**: 242-246

11 **Perry KA**, Enestvedt CK, Lorenzo CS, Schipper P, Schindler J, Morris CD, Nason K, Luketich JD, Hunter JG, Jobe BA. The integrity of esophagogastric junction anatomy in patients with isolated laryngopharyngeal reflux symptoms. *J Gastrointest Surg* 2008; **12**: 1880-1887

12 **Swoger J**, Ponsky J, Hicks DM, Richter JE, Abelson TI, Milstein C, Qadeer MA, Vaezi MF. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. *Clin Gastroenterol Hepatol* 2006; **4**: 433-441

S- Editor Li LF **L- Editor** O'Neill M **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.11

World J Gastrointest Surg 2009 November 30; 1(1): 11-15
ISSN 1948-9366 (online)

OBSERVATION

Rates of surgical site infection as a performance measure: Are we ready?

Fernando Martín Biscione

Fernando Martín Biscione, Infectious Diseases and Tropical Medicine Postgraduate Course, Medicine High School, Minas Gerais Federal University, 30-130-100, Belo Horizonte, Minas Gerais, Brazil
Author contributions: Biscione FM solely contributed to this paper.
Correspondence to: Fernando Martín Biscione, MD, MSc, Infectious Diseases and Tropical Medicine Postgraduate Course, Medicine High School, Minas Gerais Federal University, 30-130-100, Belo Horizonte, Minas Gerais, Brazil. fernandobiscione@yahoo.com.ar
Telephone: +55-31-34099300 Fax: +55-31-33378897
Received: July 2, 2009 Revised: August 25, 2009
Accepted: September 1, 2009
Published online: November 30, 2009

Key words: Hospital-associated infections; Wound infections; Performance measure; Quality improvement; Quality assurance

Peer reviewer: Toshifumi Wakai, MD, PhD, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences,1-757 Asahimachi-dori, Chuo-ku, Niigata City, 951-8510, Japan

Biscione FM. Rates of surgical site infection as a performance measure: Are we ready? *World J Gastrointest Surg* 2009; 1(1): 11-15 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/11.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.11

Abstract

With the introduction of quality assurance in health care delivery, there has been a proliferation of research studies that compare patient outcomes for similar conditions among many health care delivery facilities. Since the 1990s, increasing interest has been placed in the incorporation of clinical adverse events as quality indicators in hospital quality assurance programs. Adverse post-operative events, and very especially surgical site infection (SSI) rates after specific procedures, gained popularity as hospital quality indicators in the 1980s. For a SSI rate to be considered a valid indicator of the quality of care, it is essential that a proper adjustment for patient case mix be performed, so that meaningful comparisons of SSI rates can be made among surgeons, institutions, or over time. So far, a significant impediment to developing meaningful hospital-acquired infection rates that can be used for intra- and inter-hospital comparisons has been the lack of an adequate means of adjusting for case mix. This paper discusses what we have learned in the last years regarding risk adjustment of SSI rates for provider performance assessment, and identifies areas in which significant improvement is still needed.

INTRODUCTION

Surgical site infections (SSIs) continue to occur and remain a significant cause of disability among operated patients, in spite of the substantial advances in our understanding of their epidemiology, pathogenesis, and prevention. This short review is intended to explain how the occurrence of SSI has emerged as a quality indicator in hospital quality assurance programmes worldwide. Current limitations of SSI as a benchmarking tool and areas of further research are identified.

HOSPITAL-ACQUIRED INFECTION RATES AS PERFORMANCE MEASURES

In the past two decades, we have witnessed striking changes in the way healthcare systems supply medical services and patients purchase those services. The recognition that patients may be exposed to preventable process mistakes that may be potentially harmful for their health (specially during hospitalization), as well as the rising costs of healthcare, have shaped an effervescent atmosphere characterized by the increasing

demand for hospital performance measures and quality assurance programs by governments and consumers[1,2].

Medical mistakes and accidents that lead, or may lead, to injury during the course of patient assistance have been known to occur for a long time; however, their real magnitude and consequences have been recognized only recently. Similarly, although the concept of measuring and monitoring adverse events that arise in hospitalized patients as direct or indirect consequence of medical assistance was initiated more than three decades ago[3], the term "adverse event" only gained popularity and substance since 1991, with the publication of the shocking Harvard Medical Practice Study I (HMPS-I) by Brennan *et al*[4]. This was the very first, large-scaled study to measure and quantify with scientific accuracy the prevalence of adverse events and medical negligence in hospitalized patients[4,5]. In the HMPS-I study, over 30 000 medical records of non-psychiatric patients discharged from 51 acute care hospitals in New York State in 1984 were randomly sampled and reviewed for evidence of adverse events and negligence[4]. An adverse event was defined as an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalization, produced a disability at the time of discharge, or both. Negligence was deemed to occur when the care provided to the patient fell below the standard expected of physicians in the community. The authors identified that the statewide incidence rate of adverse events was 3.7%, with 27.6% of these adverse events due to negligence. Although 70.5% of adverse events led to minor or moderate health impairment with complete recovery, 2.6% caused permanent total disability and 13.6% caused death[4].

One decade later, the international medical community was once again shocked with the publication of the report "To Err is Human: Building a Safer Health System", by the US Institute of Medicine[6]. This report identified that preventable medical mistakes occurred with high frequency in hospitals in the US and abroad, and were responsible for annual costs in the billions, prolongation of hospital stay, and permanent and severe physical disability. It was estimated that about 7% of hospitalized patients are exposed to potential harm from medication errors, and up to 17% of patients admitted to an intensive care unit may eventually suffer a severe adverse event[6]. Largely based on the results of the HMPS-I study, the number of deaths attributable to preventable medical adverse events in US hospitals was conservatively estimated to lay somewhere between 44 000 and 98 000 per year, exceeding the number of deaths due to car crash, breast cancer, or AIDS[6].

After this report, the recommendation to expand reporting of serious adverse events and medical errors, particularly mandatory reporting, received attention[7]. Mandatory public disclosure of hospital performance measures was further catalyzed by demands from consumers, who began to argue that healthcare system users have the right to know about adverse events and the performance of healthcare providers[7]. Until 2002, only 20 states in the US had mandatory reporting systems for hospital adverse events, with the type of adverse event reported varying widely[7]. Prior to 2004, only two states (Pennsylvania and Illinois) had legislation that required healthcare providers to collect and publicly disclose healthcare-associated infection (HAI) rates, including SSI rates[8,9]. In 2004, two additional states, Missouri and Florida, passed disclosure laws[8,9]. As of March 2006, the number of states had raised to seven[10] and, by the end of 2006, laws for mandatory public reporting of HAI rates had been enacted in 15 states[11]. The specific objective of mandatory public reporting is the comparison of performance between different healthcare providers[8]. The comparison of HAI rates between hospitals and countries is often used to draw conclusions about the quality of healthcare and infection control practice[12]. Despite this, there are no controlled published data demonstrating that public reporting of rates of HAI, SSI or other adverse events improves patient outcome or the performance of healthcare providers.

RATES OF SSI AS QUALITY INDICATORS

With the introduction of quality assurance in health care delivery, there has been a proliferation of research studies that compare patient outcomes for similar conditions among many health care delivery facilities. Since the 1990s, increasing interest has been placed in the incorporation of clinical adverse events as quality indicators in hospital quality assurance programs[5]. Adverse post-operative events, and very specially SSI rates after specific procedures, gained popularity as hospital quality indicators in the 1980s[13,14], and are currently some of the most widely used hospital quality indicators worldwide[5,15-17]. Other outcomes or processes frequently proposed as measures of quality in surgical care include postoperative mortality, postoperative long-term survival, postoperative functional status and health-related quality of life, other postoperative morbidity (e.g. anastomotic leak, deep vein thrombosis), patient satisfaction, postoperative length of stay, costs, and access[5,18]. Robust evidence shows that programs for continuous quality improvement in surgical care, based on the measurement and monitoring of outcome-based and process-based quality indicators, with periodic feedback to providers and managers, can be very effective in reducing post-operative complications, patient mortality, and costs[19-22].

The public health importance of a health-related adverse event, and the need to have that event under strict surveillance, are determined by both quantitative and qualitative parameters, which can be summarized as follows[23,24]: (1) the frequency with which the event occurs in the population under study (as measured, for instance, by the incidence or prevalence rates); (2) the severity of the disability that the event causes in the patients (as measured, for instance, by the prolongation of hospital stay, impairment in quality of life, mortality, *etc.*); (3) the extent to which the adverse event can be prevented or mitigated by applying scientifically validated clinical

guidelines or all which is considered good clinical practice by the scientific community; (4) the direct and indirect costs associated with the occurrence of the adverse event; (5) the public interest; (6) the availability of a methodology for the accurate and timely detection of the event; (7) when this event is to be used as a performance measure, the availability of an accurate methodology to adjust for differences in the distribution of factors that determine the risk of developing the event. Although no quality indicator simultaneously fulfills all these criteria, the rates of SSI after selected surgical procedures and the rates of central venous catheter-associated bloodstream infections are considered to meet most of these requirements[9]. Accordingly, the measurement and monitoring of the occurrence of these HAI, as well as the adherence of healthcare providers to recommended practices to prevent the development of these infections (e.g. appropriate insertion of central venous catheters, surgical antimicrobial prophylaxis, *etc.*) are considered to be priorities[9]. Some authors argue, however, that the uncertainty about the "preventable fraction" of HAIs (i.e. how much the rate of a HAI can be reduced by maximum prevention efforts) and our current empirical limitations in risk adjustment methodologies create ambiguity about using infection rates to determine whether infection-prevention efforts are adequate in a given facility or unit[25].

THE NEED TO ADJUST THE RATES OF SSI FOR CASE MIX

Identifying groups of patients with different risk of developing an SSI may serve two distinct, but related, purposes. First, by stratifying patients according to their risk of developing an SSI, one can improve the efficiency of surveillance programmes by identifying high-risk patients and performing targeted surveillance on the group of selected patients. Second, SSI risk-adjustment allows for meaningful comparison or SSI rates among institutions or surgeons. In the remainder of this section, we shall focus on the second point.

Practicing surgeons know well that the risk of a patient developing an SSI is hard to predict. Very often, patients in which several risk factors are present do not develop an SSI, and patients in which an SSI was not among the expected adverse outcomes eventually develop an infection. This not only reflects the difficulty in predicting SSI risk on an individual basis, but also reflects the more general difficulty in predicting SSI occurrence in a given population. The risk of developing an SSI is influenced by the complex interaction of factors present before, during and after the surgical procedure[26]. These factors represent characteristics inherent in the procedure and the surgical theatre (the so called extrinsic factors) and factors inherent to the patients (the so called intrinsic factors)[26,27]. The factors already reported to influence (i.e. increase or decrease) the risk of developing an SSI amount to a very large number. Depending on the particular distribution of known (or unknown) risk factors for SSI in each patient sample, two or more hospitals or surgeons may experience different rates of SSI due to reasons other than the quality of surgical care provided to their patients. Thus, for a SSI rate to be considered a valid indicator of the quality of care, it is essential that a proper adjustment for patient case mix be performed, so that meaningful comparisons of SSI rates can be made among surgeons, institutions, or over time[28,29]. So far, a significant hindrance to developing meaningful hospital-acquired infection rates that can be used for intra- and inter-hospital comparisons has been the lack of an adequate means of adjusting for case mix[28,29]. Adjusting an infection rate for case mix is the process by which the effects of the differences in the composition (i.e. the distribution of risk factors) of the populations that are being compared are minimized through statistical methods[18]. In this context, the comparison of crude rates of SSI (i.e. without adjustment for case mix) may lead to meaningless conclusions about the quality of care provided by a hospital and, more generally speaking, about its performance[30]. Currently, organizations such as the Society for Healthcare Epidemiology of America (SHEA), the Association for Professionals in Infection Control and Epidemiology (APIC) and the Hospital Infection Control Practices Advisory Committee (HICPAC) recommend that, for purposes of public or private reporting, only rates of HAI that incorporate an adjustment for infection risk be reported[8,9,11]. In the specific case of SSI rates, the use of the National Nosocomial Infections Surveillance (NNIS) system index for adjusting the risk of infection is advised[8,9,11].

THE NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE RISK INDEX

There are a number of requirements that a SSI risk-adjustment methodology should meet if it is to be used for routine epidemiologic surveillance[27-29]. Ideally, an SSI risk-adjustment methodology should be: (1) clinically credible, in the sense that it adjusts the risk of infection for factors for which a relationship with the risk of infection is clinically easy to understand; (2) accurate; (3) simple (for example, an additive scale); (4) applicable to all patients and surgical procedures at the end of the surgery; (5) composed by a reduced number of significant variables, easily measurable and collectable; (6) transportable, that is, it should be prospectively validated on specific services or in individual hospitals to document that it predicts a patient's risk of SSI accurately in populations other than that in which it was developed; (7) above all, it should be clinically effective, in the sense that it provides useful additional information to clinicians, for instance, in terms of discrimination[27-29].

So far, no published SSI risk-adjustment methodology fulfills all these requirements. The most extensively used SSI risk-adjustment methodology worldwide is the NNIS system's risk index, described in 1991 by Culver *et al*[28]. Briefly, the NNIS system's risk index includes 3 risk factors for SSI: an American Society of Anesthesiologists' physical status preoperative score of 3, 4, or 5; a surgical wound classified as contaminated or as dirty or infected; and an

operation lasting more than *T* hours, with *T* representing the approximate 75th percentile of duration of surgery and depending on the surgical procedure performed[28]. For cholecystectomy, colon surgery, appendectomy and gastric surgery, the surgical approach (laparoscopic or open) is also incorporated in the score[31]. The NNIS system's risk index is procedure specific, which means that SSI risk strata are calculated for pre-specified surgical procedure categories. Each factor present in the patient by the end of the surgery adds one point, and the sum over all factors determines the SSI risk stratum in which the patient is placed: 0 through 4 for cholecystectomy, colon surgery, appendectomy and gastric surgery; and 0 through 3 for all other procedure categories[31].

Although this index is indeed clinically credible, simple, and composed by few variables easily measurable and collectable at the end of the surgery, its transportability and clinical effectiveness has not been extensively evaluated outside US hospitals[32]. The problem of transportability is of paramount importance. If a model developed at one site does not apply at other sites, then these facilities may receive a rating better or worse than they deserve. Therefore, the use of such models at facilities other than at those where they were developed should initially involve the careful application of validation techniques to identify specific areas of inconsistency between predictions and outcomes[33]. Another problem with the use of such models is that with rapid changes in clinical practices over time, any predictive model for patient outcome may have limited life. To use the model over a lengthy period, one should conduct routine validation and update at regular intervals to ensure that conditions in the validation population have not changed[33]. This is especially true for the NNIS system's SSI risk index: this index was described almost two decades ago and, since then, we have experienced dramatic changes regarding pre- and postoperative strategies for the prevention of SSIs. One of these changes is illustrated by the decreasing length of hospital postoperative stay. In the last decades, we have progressively moved to shorter and shorter postoperative hospital stays, so an ever increasing number of SSI are becoming evident after the patient has been discharged from the hospital[34]. The NNIS risk index was developed at a time in which few hospitals around the world had post discharge SSI surveillance programs. In fact, the original validation of the NNIS risk index was performed in a sample of hospitals in which only 30% of them had some kind of post discharge surveillance strategy[28]. So, at first glance, the NNIS risk index would be suitable for assessing in-hospital SSI risk. In recent years, some evidence has accumulated showing that the factors classically associated with SSI occurrence before hospital discharge are poor predictors of the infections that develop after hospital discharge[35,36]. To date, however, no systematic evaluation has been conducted to assess the impact of the SSIs diagnosed after hospital discharge on the performance of the NNIS risk index.

Another empirical challenge for SSI risk-adjustment models is the problem of incomplete post-discharge follow-up. Unfortunately, post discharge surveillance of SSI is laborious, time-consuming and costly, but without structured post discharge surveillance efforts, these infections will be missed. In the NNIS risk index, patients not reached by post discharge surveillance are counted as uninfected (provided that they did not develop the infection during hospital stay)[31], artificially reducing the measured SSI risk. The problem of incomplete follow-up after discharge has been largely overlooked in SSI risk-modeling, and there are few reports in the literature in which the problem of missing post discharge information has been explicitly accounted for[37-42]. In a recent study[43], we have found that incorporating a post discharge surveillance indicator to the NNIS risk index can add potentially useful clinical information, although concerns about the mechanism that leads to missing post discharge information must be borne in mind.

CONCLUSION

Surveillance of HAI is an indispensable tool in infection control. The need to compare rates in one institution with those in others has led to the development of national surveillance systems and risk-stratification models. A great deal of progress toward comparability of SSI rates has been made, but the problem of risk stratification for the purposes of comparing patient populations are still under debate and need further research.

REFERENCES

1 Institute of Medicine. Crossing the quality chasm: a new health system for the twenty-first century. Washington, DC: National Academies Press, 2001
2 **Chassin MR**, Galvin RW. The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. *JAMA* 1998; **280**: 1000-1005
3 **Donaldson MS**. Institute of Medicine. Statement on Quality of Care. Washington, DC: National Academies Press, 1998
4 **Brennan TA**, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, Newhouse JP, Weiler PC, Hiatt HH. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med* 1991; **324**: 370-376
5 **Bruce J**, Russell EM, Mollison J, Krukowski ZH. The measurement and monitoring of surgical adverse events. *Health Technol Assess* 2001; **5**: 1-194
6 **Kohn LT**, Corrigan JM, Donaldson MS. Institute of Medicine. To Err Is Human: Building A Safer Health System. Washington, DC: National Academies Press, 2000
7 **Leape LL**. Reporting of adverse events. *N Engl J Med* 2002; **347**: 1633-1638
8 **Wong ES**, Rupp ME, Mermel L, Perl TM, Bradley S, Ramsey KM, Ostrowsky B, Valenti AJ, Jernigan JA, Voss A, Tapper ML. Public disclosure of healthcare-associated infections: the role of the Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 2005; **26**: 210-212
9 **McKibben L**, Horan TC, Tokars JI, Fowler G, Cardo DM, Pearson ML, Brennan PJ. Guidance on public reporting of healthcare-associated infections: recommendations of the Healthcare Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 2005; **26**: 580-587
10 **Klevens RM**, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, Cardo DM. Estimating health care-associated infections and deaths in U.S. hospitals, 2002.

Public Health Rep 2007; **122**: 160-166
11 **Association for Professionals in Infection Control and Epidemiology**. Mandatory public reporting of healthcare-associated infections. Washington, DC: APIC, 2007
12 **Wilson J**, Ramboer I, Suetens C. Hospitals in Europe Link for Infection Control through Surveillance (HELICS). Inter-country comparison of rates of surgical site infection--opportunities and limitations. *J Hosp Infect* 2007; **65** Suppl 2: 165-170
13 **Larson E**, Oram LF, Hedrick E. Nosocomial infection rates as an indicator of quality. *Med Care* 1988; **26**: 676-684
14 **Patterson CH**. Perceptions and misconceptions regarding the Joint Commission's view of quality monitoring. *Am J Infect Control* 1989; **17**: 231-240
15 **Reilly JS**, Baird D, Hill R. The importance of definitions and methods in surgical wound infection audit. *J Hosp Infect* 2001; **47**: 64-66
16 **Dimick JB**, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004; **199**: 531-537
17 **Khuri SF**, Daley J, Henderson W, Hur K, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, Irvin G 3rd, McDonald G, Passaro E Jr, Phillips L, Scamman F, Spencer J, Stremple JF. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. *Ann Surg* 1998; **228**: 491-507
18 **Daley J**, Henderson WG, Khuri SF. Risk-adjusted surgical outcomes. *Annu Rev Med* 2001; **52**: 275-287
19 **Hannan EL**, Kilburn H Jr, Racz M, Shields E, Chassin MR. Improving the outcomes of coronary artery bypass surgery in New York State. *JAMA* 1994; **271**: 761-766
20 **Khuri SF**, Daley J, Henderson WG. The comparative assessment and improvement of quality of surgical care in the Department of Veterans Affairs. *Arch Surg* 2002; **137**: 20-27
21 **O'Connor GT**, Plume SK, Olmstead EM, Morton JR, Maloney CT, Nugent WC, Hernandez F Jr, Clough R, Leavitt BJ, Coffin LH, Marrin CA, Wennberg D, Birkmeyer JD, Charlesworth DC, Malenka DJ, Quinton HB, Kasper JF. A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *JAMA* 1996; **275**: 841-846
22 **Grover FL**, Cleveland JC Jr, Shroyer LW. Quality improvement in cardiac care. *Arch Surg* 2002; **137**: 28-36
23 **German RR**, Lee LM, Horan JM, Milstein RL, Pertowski CA, Waller MN. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. *MMWR Recomm Rep* 2001; **50**: 1-35; quiz CE1-CE7
24 **Teutsch SM**, Thacker SB. Planning a public health surveillance system. *Epidemiol Bull* 1995; **16**: 1-6
25 **Tokars JI**, Richards C, Andrus M, Klevens M, Curtis A, Horan T, Jernigan J, Cardo D. The changing face of surveillance for health care-associated infections. *Clin Infect Dis* 2004; **39**: 1347-1352
26 **Mangram AJ**, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999; **20**: 250-278; quiz 279-280
27 **Roy MC**, Perl TM. Basics of surgical-site infection surveillance. *Infect Control Hosp Epidemiol* 1997; **18**: 659-668
28 **Culver DH**, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, Banerjee SN, Edwards JR, Tolson JS, Henderson TS. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med* 1991; **91**: 152S-157S
29 **Gaynes RP**, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992-1998: the National Nosocomial Infections Surveillance System basic SSI risk index. *Clin Infect Dis* 2001; **33** Suppl 2: S69-S77
30 Nosocomial infection rates for interhospital comparison: limitations and possible solutions. A Report from the National Nosocomial Infections Surveillance (NNIS) System. *Infect Control Hosp Epidemiol* 1991; **12**: 609-621
31 National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; **32**: 470-485
32 **Vandenbroucke-Grauls C**, Schultsz C. Surveillance in infection control: are we making progress? *Curr Opin Infect Dis* 2002; **15**: 415-419
33 **Miller ME**, Hui SL, Tierney WM. Validation techniques for logistic regression models. *Stat Med* 1991; **10**: 1213-1226
34 **Petherick ES**, Dalton JE, Moore PJ, Cullum N. Methods for identifying surgical wound infection after discharge from hospital: a systematic review. *BMC Infect Dis* 2006; **6**: 170
35 **Medina-Cuadros M**, Sillero-Arenas M, Martínez-Gallego G, Delgado-Rodríguez M. Surgical wound infections diagnosed after discharge from hospital: epidemiologic differences with in-hospital infections. *Am J Infect Control* 1996; **24**: 421-428
36 **Delgado-Rodríguez M**, Gómez-Ortega A, Sillero-Arenas M, Llorca J. Epidemiology of surgical-site infections diagnosed after hospital discharge: a prospective cohort study. *Infect Control Hosp Epidemiol* 2001; **22**: 24-30
37 **Thibon P**, Parienti JJ, Borgey F, Le Prieur A, Bernet C, Branger B, Le Coutour X. Use of censored data to monitor surgical-site infections. *Infect Control Hosp Epidemiol* 2002; **23**: 368-371
38 **Rioux C**, Grandbastien B, Astagneau P. The standardized incidence ratio as a reliable tool for surgical site infection surveillance. *Infect Control Hosp Epidemiol* 2006; **27**: 817-824
39 **Geubbels EL**, Grobbee DE, Vandenbroucke-Grauls CM, Wille JC, de Boer AS. Improved risk adjustment for comparison of surgical site infection rates. *Infect Control Hosp Epidemiol* 2006; **27**: 1330-1339
40 **Geubbels EL**, Nagelkerke NJ, Mintjes-De Groot AJ, Vandenbroucke-Grauls CM, Grobbee DE, De Boer AS. Reduced risk of surgical site infections through surveillance in a network. *Int J Qual Health Care* 2006; **18**: 127-133
41 **Biscione FM**, Couto RC, Pedrosa TM, Neto MC. Comparison of the risk of surgical site infection after laparoscopic cholecystectomy and open cholecystectomy. *Infect Control Hosp Epidemiol* 2007; **28**: 1103-1106
42 **Biscione FM**, Couto RC, Pedrosa TM, Neto MC. Factors influencing the risk of surgical site infection following diagnostic exploration of the abdominal cavity. *J Infect* 2007; **55**: 317-323
43 **Biscione FM**, Couto RC, Pedrosa TM. Accounting for incomplete post discharge follow-up during surveillance of surgical site infection by use of the National Nosocomial Infections Surveillance system's risk index. *Infect Control Hosp Epidemiol* 2009; **30**: 433-439

S- Editor Li LF **L- Editor** Lalor PF **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.16

World J Gastrointest Surg 2009 November 30; 1(1): 16-20
ISSN 1948-9366 (online)

GUIDELINES FOR CLINICAL PRACTICE

Pancreatic islet transplantation

Hirofumi Noguchi

Hirofumi Noguchi, Regenerative Research Islet Cell Transplant Program, Baylor All Saints Medical Center, Baylor Research Institute, Fort Worth, TX 76104, United States
Author contributions: Noguchi H solely contributed to this paper.
Supported by The All Saints Health Foundation (in part)
Correspondence to: Hirofumi Noguchi, MD, PhD, Regenerative Research Islet Cell Transplant Program, Baylor All Saints Medical Center, Baylor Research Institute, 1400 8th Avenue, Fort Worth, TX 76104, United States. hirofumn@baylorhealth.edu
Telephone: +1-214-8209016 Fax: +1-214-8204952
Received: October 29, 2009 Revised: November 10, 2009
Accepted: November 17, 2009
Published online: November 30, 2009

Key words: Pancreatic islet transplantation; Islet isolation; Pancreatic β-cells; Islet regeneration

Peer reviewer: Stefano Crippa, MD, Department of Surgery, University of Verona, Policlinico "GB Rossi", Piazzale LA Scuro, 10, 37134 Verona, Italy

Noguchi H. Pancreatic islet transplantation. *World J Gastrointest Surg* 2009; 1(1): 16-20 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/16.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.16

Abstract

Type 1 diabetes mellitus is an autoimmune disease, which results in the permanent destruction of β-cells of the pancreatic islets of Langerhans. While exogenous insulin therapy has dramatically improved the quality of life, chronic diabetic complications develop in a substantial proportion of subjects and these complications generally progress and worsen over time. Although intensive insulin therapy has proven effective to delay and sometimes prevent the progression of complications such as nephropathy, neuropathy or retinopathy, it is difficult to achieve and maintain long term in most subjects. Reasons for this difficulty include compliance issues and the increased risk of severe hypoglycemic episodes, which are generally associated with intensification of exogenous insulin therapy. Clinical studies have shown that transplantation of pancreas or purified pancreatic islets can support glucose homeostasis in type 1 diabetic patients. Islet transplantation carries the special advantages of being less invasive and resulting in fewer complications compared with the traditional pancreas or pancreas-kidney transplantation. However, islet transplantation efforts have limitations including the short supply of donor pancreata, the paucity of experienced islet isolation teams, side effects of immunosuppressants and poor long-term results. The purpose of this article is to review recent progress in clinical islet transplantation for the treatment of diabetes.

INTRODUCTION

The primary treatment for type 1 diabetes is multiple injections of exogenous insulin together with regular monitoring of blood glucose levels. Intensive insulin therapy can help prevent long-term diabetic complications and the introduction of insulin pumps into clinical practice has raised the possibility of mimicking the basic, endogenous insulin secretion pattern, which directly relates to a better glycemic control[1-3]. Despite appropriate treatment, satisfactory and safe control of blood glucose levels still cannot be achieved in a small percentage of patients. Pancreatic islet transplantation has recently emerged as one of the most promising therapeutic approaches for improving glycometabolic control in type 1 diabetic patients. The first successful series of islet allografts was reported in 1990 in surgical diabetes[4], while the results in type 1 diabetes slowly improved during the 1990s until 1999. In 2000, the "Edmonton Protocol" introduced several modifications to the transplantation procedure, such as the use of a steroid-free immunosuppression regimen and transplantation of a mean islet mass of 11 000 islet equivalents per kilogram of patient's weight[5]. Since this exciting report, clinical islet transplantation activity has dramatically increased all over the world. A multi-center trial to evaluate the reproducibility of the Edmonton study organized by the Immune Tolerance Network reported variable rates of

success, indicating that the complexity of the procedure should not be underestimated by new centers entering the field[6]. In the centers with the most experience in the procedure, approximately 80% of patients treated with islet transplantation achieved insulin independence within the first year post-transplantation[6]. However, the Edmonton group showed in 2005 that only 7.5% of the 65 patients who received islet transplantation have reached insulin independence, although the majority of patients (82%) presented graft survival (C-peptide positivity)[7]. The data indicated the need of further advances in the preservation of the function of transplanted islets. Islet transplantation still faces major challenges, especially those related to cell loss during the process of islet isolation and the losses related to the graft site, apoptosis, allorejection, autoimmunity, and immunosuppression.

This review describes recent progress in clinical islet transplantation for the treatment of diabetes.

PANCREAS PROCUREMENT AND PRESERVATION

Pancreata are procured using a standardized technique in whole pancreas transplantation to minimize warm ischemia. University of Wisconsin (UW) solution is used for *in situ* perfusion of the donor. The pancreas is excised immediately after the liver and before the kidneys and is normally preserved in UW solution[8,9].

We recently reported that the ductal injection of 1 mL/g pancreas weight of a new preservation solution (modified Kyoto (MK) solution) before pancreas storage improves islet yields[10,11]. MK solution contains trehalose and ulinastatin as distinct components. Trehalose has a cytoprotective effect against stress, and ulinastatin inhibits trypsin. Ductal injection of the preservation solution increased the ATP level in pancreas tissue, reduced trypsin activity during the digestion step, and prevented islet apoptosis[10]. These data suggest that the ductal injection of preservation solution leads to improved outcomes for pancreatic islet transplantation.

Kuroda *et al*[12] were the first to report that the two-layer preservation method, in which the pancreas is stored at the interface of UW solution and oxygenated perfluorochemical (PFC), is effective for pancreas preservation. Since then, the two-layer method has been utilized for many clinical trials in islet transplantation[13-16]. However, UW solution has several disadvantages, including the inhibition of Liberase activity. We investigated the features of MK solution[17]. In porcine islet isolation, islet yield was significantly higher in the MK/PFC group compared with the UW/PFC group. Compared with UW solution, MK solution significantly inhibited trypsin activity in the digestion step; moreover, MK solution inhibited collagenase digestion less than UW solution. These data suggest that pancreas preservation with MK solution improves islet yield by trypsin inhibition and causing less collagenase inhibition.

ISLET DIGESTION

Human islet isolation is conducted using the standard Ricordi technique with modifications introduced in the Edmonton protocol. The introduction of the semi-automated method for controlled pancreatic digestion using a dissociation chamber (Ricordi Chamber) has dramatically increased islet yields from human pancreata[18] and the general principles of this method still form the basis of current islet isolation technology[19-22]. After perfusion through the pancreatic duct in a controlled fashion with a cold enzyme blend of collagenase with neutral protease, the distended pancreas is then cut into 7 to 9 pieces, placed in a Ricordi chamber, and shaken gently. While the pancreas is being digested by re-circulating the enzyme solution through the Ricordi chamber at 37℃, we monitor the extent of digestion with dithizone staining by taking small samples from the system. Once digestion is confirmed to be complete, dilution solution is introduced into the system. Then, the system is cooled to stop further digestive activity. The digested tissue is collected in conical tubes containing 25% HSA and washed with fresh medium to remove the enzyme.

ISLET PURIFICATION

Islet purification minimizes the risks associated with islet infusion through the portal vein by reducing the amount of transplanted tissue. Large-scale continuous purification using the COBE2991 cell processor, with Ficoll solutions, is the current gold standard method[20-24]. Recently, the Ficoll-based gradient has been progressively replaced by iodixanol-based gradients[16,22,25]. We recently showed the effectiveness of iodixanol-controlled density gradients on the islet purification step[25]. Islet yield after purification and rate of post-purification recovery were significantly higher using iodixanol-based solutions than with standard continuous gradient purification by Ficoll solutions. The data suggest that using an iodixanol-controlled density gradient improves the islet recovery rate in human islet isolation.

Recently, Ichii *et al*[26] have reported that an additional gradient purification method following regular purification with bottom loading could be of assistance in maximizing the number of islet preparations successfully used for transplantation by improving the efficiency of the purification of trapped islets, which often come from younger donor pancreata. This supplemental purification following regular purification could maximize the islet yield and improve clinical islet transplantation.

ISLET CULTURE/PRESERVATION

Culturing islets prior to transplantation provides flexibility for evaluation of isolated islets and pre-treatment of patients. However, it is well known that isolated islets deteriorate rapidly in culture. Optimum culture conditions

should provide sufficient oxygen and nutrients, in order to allow islet cells to recover from isolation-induced damage, maintain the three-dimensional structure of the clusters and reduce islet mass loss. Although the Edmonton protocol required freshly isolated islets to be transplanted without keeping them in culture[5], most transplant centers culture isolated human islet preparations before transplantation[7,16,21,23,34,27-29].

We evaluated optimal temperature for culture/preservation of isolated human islets before transplantation. Isolated islets were cultured or preserved for 48 h in the following culture/preservation conditions: preservation at 4℃ in UW solution, culture at 22℃ or 37℃ in culture medium. Islet morphology after 4℃ preservation was similar to that of fresh islets, whereas islet diameter after 37℃ or 22℃ culture was smaller than that of fresh islets. Islet yield significantly decreased at higher temperatures (24% loss in 37℃ culture and 19% loss in 22℃ culture, but less than 5% loss in 4℃ preservation). When cultured/preserved islets were transplanted into diabetic nude mice, the attainability of post-transplantation normoglycemia was significantly higher in the 4℃ preservation group than in 22℃ and 37℃ culture groups. These data suggest that preservation of isolated islets at 4℃ improves the outcome of islet transplantation more efficiently than preservation at either 22℃ or 37℃[30].

ISLET TRANSPLANTATION

Isolated islets are transplanted into the recipient liver through the portal vein with a percutaneous transhepatic cannulation under sonographic and fluoroscopic guidance[31]. The potential complications of the method include portal vein thrombosis, portal hypertension, and bleeding[32,33]. Heparin has been added to the process in order to reduce the clotting process, termed the instant blood mediated inflammatory reaction (IBMIR)[34,35]. Moreover, the use of heparin or anti-coagulative agents for several days following islet transplantation, together with intensive insulin treatment for the first weeks after transplantation have recently been reported as critically important variables which improve the efficiency of initial islet engraftment.

IMMUNOSUPPRESSION

A steroid-free immunosuppressive protocol with a combination of sirolimus and tacrolimus, which the Edmonton group reported, has been utilized in many clinical islet transplant trials. Although short-term results of islet transplantation using this protocol have been promising, with approximately 80% of patients maintaining insulin independence at 1 year posttransplant, the proportion of recipients maintaining insulin independence declines after the first year posttransplant[7,20]. The reason for this decline remains unclear, but suggested causes include alloimmune rejection, autoimmune recurrence, and/or toxicity of immunosuppressive medications[36,37]. Allo/autoimmunity and drug toxicity may be ameliorated by refined immunosuppressive protocols.

Bellin *et al*[38], recently showed improved success with a modified immunosuppressive protocol, usage of antithymocyte globulin (ATG) plus etanercept as induction therapy. Recipients received cyclosporine and everolimus for maintenance immunosuppression for the first year posttransplant, with mycophenolic acid or mycophenolate mofetil subsequently substituted for everolimus. Four of six recipients who received islet transplantation maintained insulin independence for more than 3 years. These results suggest that modifications of immunosuppressive protocol have been a key to improve long-term graft survival.

CONCLUSION

Islet transplantation is an alternative method to whole pancreas transplantation in patients with type 1 diabetes because of its low invasiveness and safety to the recipient[39,40]. Significant progress in clinical islet transplantation has occurred during recent years, with a progressive improvement of short-term and long term outcomes. The most recent results indicate that islet transplant recipients can maintain islet graft function without deterioration beyond 5 years, progressively closing the gap with the results of whole organ, pancreas transplantation. Although experiments in β-cell regeneration from stem cells are ongoing[41-48], there is still no reliable method to generate β-cells. Until a new method to generate β-cells is developed, improving the efficacy of islet transplantation seems the most realistic and prudent method to cure diabetes.

ACKNOWLEDGMENTS

The author thanks Dr. Steven Phillips for editing the manuscript.

REFERENCES

1 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; **329**: 977-986
2 The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial. *Arch Ophthalmol* 1995; **113**: 36-51
3 **Dufrane D**, Gianello P. Pig islet xenotransplantation into non-human primate model. *Transplantation* 2008; **86**: 753-760
4 **Tzakis AG**, Ricordi C, Alejandro R, Zeng Y, Fung JJ, Todo S, Demetris AJ, Mintz DH, Starzl TE. Pancreatic islet transplantation after upper abdominal exenteration and liver replacement. *Lancet* 1990; **336**: 402-405
5 **Shapiro AM**, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; **343**: 230-238
6 **Shapiro AM**, Ricordi C, Hering B. Edmonton's islet success has indeed been replicated elsewhere. *Lancet* 2003; **362**: 1242
7 **Ryan EA**, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005; **54**: 2060-2069

8 **D'Alessandro AM**, Stratta RJ, Sollinger HW, Kalayoglu M, Pirsch JD, Belzer FO. Use of UW solution in pancreas transplantation. *Diabetes* 1989; **38** Suppl 1: 7-9

9 **Munn SR**, Kaufman DB, Field MJ, Viste AB, Sutherland DE. Cold-storage preservation of the canine and rat pancreas prior to islet isolation. *Transplantation* 1989; **47**: 28-31

10 **Noguchi H**, Ueda M, Hayashi S, Kobayashi N, Okitsu T, Iwanaga Y, Nagata H, Nakai Y, Matsumoto S. Ductal injection of preservation solution increases islet yields in islet isolation and improves islet graft function. *Cell Transplant* 2008; **17**: 69-81

11 **Matsumoto S**, Noguchi H, Shimoda M, Ikemoto T, Naziruddin B, Jackson A, Tamura Y, Greg O, Fujita Y, Chujo D, Takita T, Kobayashi N, Onaca N, Levy MF. Seven consecutive successful clinical islet isolations with pancreatic dictal injection. *Cell Transplant* 2009; In press

12 **Kuroda Y**, Kawamura T, Suzuki Y, Fujiwara H, Yamamoto K, Saitoh Y. A new, simple method for cold storage of the pancreas using perfluorochemical. *Transplantation* 1988; **46**: 457-460

13 **Matsumoto S**, Qualley SA, Goel S, Hagman DK, Sweet IR, Poitout V, Strong DM, Robertson RP, Reems JA. Effect of the two-layer (University of Wisconsin solution-perfluorochemical plus O2) method of pancreas preservation on human islet isolation, as assessed by the Edmonton Isolation Protocol. *Transplantation* 2002; **74**: 1414-1419

14 **Tsujimura T**, Kuroda Y, Kin T, Avila JG, Rajotte RV, Korbutt GS, Ryan EA, Shapiro AM, Lakey JR. Human islet transplantation from pancreases with prolonged cold ischemia using additional preservation by the two-layer (UW solution/perfluorochemical) cold-storage method. *Transplantation* 2002; **74**: 1687-1691

15 **Ricordi C**, Fraker C, Szust J, Al-Abdullah I, Poggioli R, Kirlew T, Khan A, Alejandro R. Improved human islet isolation outcome from marginal donors following addition of oxygenated perfluorocarbon to the cold-storage solution. *Transplantation* 2003; **75**: 1524-1527

16 **Hering BJ**, Kandaswamy R, Harmon JV, Ansite JD, Clemmings SM, Sakai T, Paraskevas S, Eckman PM, Sageshima J, Nakano M, Sawada T, Matsumoto I, Zhang HJ, Sutherland DE, Bluestone JA. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. *Am J Transplant* 2004; **4**: 390-401

17 **Noguchi H**, Ueda M, Nakai Y, Iwanaga Y, Okitsu T, Nagata H, Yonekawa Y, Kobayashi N, Nakamura T, Wada H, Matsumoto S. Modified two-layer preservation method (M-Kyoto/PFC) improves islet yields in islet isolation. *Am J Transplant* 2006; **6**: 496-504

18 **Ricordi C**, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. *Diabetes* 1988; **37**: 413-420

19 **Ricordi C**, Strom TB. Clinical islet transplantation: advances and immunological challenges. *Nat Rev Immunol* 2004; **4**: 259-268

20 **Shapiro AM**, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med* 2006; **355**: 1318-1330

21 **Froud T**, Ricordi C, Baidal DA, Hafiz MM, Ponte G, Cure P, Pileggi A, Poggioli R, Ichii H, Khan A, Ferreira JV, Pugliese A, Esquenazi VV, Kenyon NS, Alejandro R. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. *Am J Transplant* 2005; **5**: 2037-2046

22 **Hering BJ**, Kandaswamy R, Ansite JD, Eckman PM, Nakano M, Sawada T, Matsumoto I, Ihm SH, Zhang HJ, Parkey J, Hunter DW, Sutherland DE. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA* 2005; **293**: 830-835

23 **Goto M**, Eich TM, Felldin M, Foss A, Källen R, Salmela K, Tibell A, Tufveson G, Fujimori K, Engkvist M, Korsgren O. Refinement of the automated method for human islet isolation and presentation of a closed system for in vitro islet culture. *Transplantation* 2004; **78**: 1367-1375

24 **Markmann JF**, Deng S, Huang X, Desai NM, Velidedeoglu EH, Lui C, Frank A, Markmann E, Palanjian M, Brayman K, Wolf B, Bell E, Vitamaniuk M, Doliba N, Matschinsky F, Barker CF, Naji A. Insulin independence following isolated islet transplantation and single islet infusions. *Ann Surg* 2003; **237**: 741-749; discussion 749-750

25 **Noguchi H**, Ikemoto T, Naziruddin B, Jackson A, Shimoda M, Fujita Y, Chujo D, Takita M, Kobayashi N, Onaca N, Levy MF, Matsumoto S. Iodixanol-controlled density gradient during islet purification improves recovery rate in human islet isolation. *Transplantation* 2009; **87**: 1629-1635

26 **Ichii H**, Pileggi A, Molano RD, Baidal DA, Khan A, Kuroda Y, Inverardi L, Goss JA, Alejandro R, Ricordi C. Rescue purification maximizes the use of human islet preparations for transplantation. *Am J Transplant* 2005; **5**: 21-30

27 **Nano R**, Clissi B, Melzi R, Calori G, Maffi P, Antonioli B, Marzorati S, Aldrighetti L, Freschi M, Grochowiecki T, Socci C, Secchi A, Di Carlo V, Bonifacio E, Bertuzzi F. Islet isolation for allotransplantation: variables associated with successful islet yield and graft function. *Diabetologia* 2005; **48**: 906-912

28 **Goss JA**, Schock AP, Brunicardi FC, Goodpastor SE, Garber AJ, Soltes G, Barth M, Froud T, Alejandro R, Ricordi C. Achievement of insulin independence in three consecutive type-1 diabetic patients via pancreatic islet transplantation using islets isolated at a remote islet isolation center. *Transplantation* 2002; **74**: 1761-1766

29 **Warnock GL**, Meloche RM, Thompson D, Shapiro RJ, Fung M, Ao Z, Ho S, He Z, Dai LJ, Young L, Blackburn L, Kozak S, Kim PT, Al-Adra D, Johnson JD, Liao YH, Elliott T, Verchere CB. Improved human pancreatic islet isolation for a prospective cohort study of islet transplantation vs best medical therapy in type 1 diabetes mellitus. *Arch Surg* 2005; **140**: 735-744

30 **Noguchi H**, Naziruddin B, Jackson A, Shimoda M, Ikemoto T, Fujita Y, Chujo D, Takita M, Kobayashi N, Onaca N, Levy MF, Matsumoto S. Low-temperature preservation of isolated islets is superior to conventional islet culture before islet transplantation. *Transplantaiton* 2009; In press

31 **Venturini M**, Angeli E, Maffi P, Fiorina P, Bertuzzi F, Salvioni M, De Cobelli F, Socci C, Aldrighetti L, Losio C, Di Carlo V, Secchi A, Del Maschio A. Technique, complications, and therapeutic efficacy of percutaneous transplantation of human pancreatic islet cells in type 1 diabetes: the role of US. *Radiology* 2005; **234**: 617-624

32 **Hafiz MM**, Faradji RN, Froud T, Pileggi A, Baidal DA, Cure P, Ponte G, Poggioli R, Cornejo A, Messinger S, Ricordi C, Alejandro R. Immunosuppression and procedure-related complications in 26 patients with type 1 diabetes mellitus receiving allogeneic islet cell transplantation. *Transplantation* 2005; **80**: 1718-1728

33 **Brennan DC**, Shannon MB, Koch MJ, Polonsky KS, Desai N, Shapiro J. Portal vein thrombosis complicating islet transplantation in a recipient with the Factor V Leiden mutation. *Transplantation* 2004; **78**: 172-173

34 **Johansson H**, Lukinius A, Moberg L, Lundgren T, Berne C, Foss A, Felldin M, Källen R, Salmela K, Tibell A, Tufveson G, Ekdahl KN, Elgue G, Korsgren O, Nilsson B. Tissue factor produced by the endocrine cells of the islets of Langerhans is associated with a negative outcome of clinical islet transplantation. *Diabetes* 2005; **54**: 1755-1762

35 **Moberg L**, Johansson H, Lukinius A, Berne C, Foss A, Källen R, Østraat Ø, Salmela K, Tibell A, Tufveson

G, Elgue G, Nilsson Ekdahl K, Korsgren O, Nilsson B. Production of tissue factor by pancreatic islet cells as a trigger of detrimental thrombotic reactions in clinical islet transplantation. *Lancet* 2002; **360**: 2039-2045

36 **Monti P**, Scirpoli M, Maffi P, Ghidoli N, De Taddeo F, Bertuzzi F, Piemonti L, Falcone M, Secchi A, Bonifacio E. Islet transplantation in patients with autoimmune diabetes induces homeostatic cytokines that expand autoreactive memory T cells. *J Clin Invest* 2008; **118**: 1806-1814

37 **Nir T**, Melton DA, Dor Y. Recovery from diabetes in mice by beta cell regeneration. *J Clin Invest* 2007; **117**: 2553-2561

38 **Bellin MD**, Kandaswamy R, Parkey J, Zhang HJ, Liu B, Ihm SH, Ansite JD, Witson J, Bansal-Pakala P, Balamurugan AN, Papas K, Sutherland DE, Moran A, Hering BJ. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. *Am J Transplant* 2008; **8**: 2463-2470

39 **Matsumoto S**, Okitsu T, Iwanaga Y, Noguchi H, Nagata H, Yonekawa Y, Yamada Y, Fukuda K, Tsukiyama K, Suzuki H, Kawasaki Y, Shimodaira M, Matsuoka K, Shibata T, Kasai Y, Maekawa T, Shapiro J, Tanaka K. Insulin independence after living-donor distal pancreatectomy and islet allotransplantation. *Lancet* 2005; **365**: 1642-1644

40 **Noguchi H**, Iwanaga Y, Okitsu T, Nagata H, Yonekawa Y, Matsumoto S. Evaluation of islet transplantation from non-heart beating donors. *Am J Transplant* 2006; **6**: 2476-2482

41 **D'Amour KA**, Bang AG, Eliazer S, Kelly OG, Agulnick AD, Smart NG, Moorman MA, Kroon E, Carpenter MK, Baetge EE. Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. *Nat Biotechnol* 2006; **24**: 1392-1401

42 **Noguchi H**. Stem cells for the treatment of diabetes. *Endocr J* 2007; **54**: 7-16

43 **Noguchi H**, Kaneto H, Weir GC, Bonner-Weir S. PDX-1 protein containing its own antennapedia-like protein transduction domain can transduce pancreatic duct and islet cells. *Diabetes* 2003; **52**: 1732-1737

44 **Kroon E**, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, Young H, Richardson M, Smart NG, Cunningham J, Agulnick AD, D'Amour KA, Carpenter MK, Baetge EE. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. *Nat Biotechnol* 2008; **26**: 443-452

45 **Noguchi H**, Oishi K, Ueda M, Yukawa H, Hayashi S, Kobayashi N, Levy MF, Matusmoto S. Establishment of mouse pancreatic stem cell line. *Cell Transplant* 2009; **18**: 563-571

46 **Noguchi H**, Bonner-Weir S, Wei FY, Matsushita M, Matsumoto S. BETA2/NeuroD protein can be transduced into cells due to an arginine- and lysine-rich sequence. *Diabetes* 2005; **54**: 2859-2866

47 **Noguchi H**, Ueda M, Matsumoto S, Kobayashi N, Hayashi S. BETA2/NeuroD protein transduction requires cell surface heparan sulfate proteoglycans. *Hum Gene Ther* 2007; **18**: 10-17

48 **Maehr R**, Chen S, Snitow M, Ludwig T, Yagasaki L, Goland R, Leibel RL, Melton DA. Generation of pluripotent stem cells from patients with type 1 diabetes. *Proc Natl Acad Sci USA* 2009; **106**: 15768-15773

S- Editor Li LF **L- Editor** Lalor PF **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.21

World J Gastrointest Surg 2009 November 30; 1(1): 21-25
ISSN 1948-9366 (online)

GUIDELINES FOR CLINICAL PRACTICE

Future of bioartificial liver support

Robert AFM Chamuleau

Robert AFM Chamuleau, Department of Hepatology, Academic Medical Center, University of Amsterdam, Meibergdreef 69-71, 1105 BK, Amsterdam, The Netherlands
Author contributions: Chamuleau RAFM contributed solely to this paper.
Correspondence to: Robert AFM Chamuleau, MD, PhD, Department of Hepatology, Academic Medical Center, S-Building, Floor 1, Room 166, Meibergdreef 69-71, 1105 BK, Amsterdam, The Netherlands. r.a.chamuleau@amc.uva.nl
Telephone: +31-20-5666832 Fax: +31-20-5669190
Received: October 21, 2009 Revised: October 28, 2009
Accepted: November 4, 2009
Published online: November 30, 2009

Abstract

Many different artificial liver support systems (biological and non-biological) have been developed, tested pre-clinically and some have been applied in clinical trials. Based on theoretical considerations a biological artificial liver (BAL) should be preferred above the non-biological ones. However, clinical application of the BAL is still experimental. Here we try to analyze which hurdles have to be taken before the BAL will become standard equipment in the intensive care unit for patients with acute liver failure or acute deterioration of chronic liver disease.

Key words: Acute liver failure; Bioartificial liver; Liver transplantation; Cell transplantation; Tissue engineering; Xenotransplantation

Peer reviewer: Dr. Gianpiero Gravante, Department of Hepatobiliary and Pancreatic Surgery, University Hospitals of Leicester, Leicester General Hospital, 38 Hospital Close, Leicester, LE54WU, United Kingdom

Chamuleau RAFM. Future of bioartificial liver support. *World J Gastrointest Surg* 2009; 1(1): 21-25 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/21.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.21

INTRODUCTION

Nowadays intensive care doctors have many artificial devices to support their patients with failing organs. They possess different types of hemodialysis devices, artificial ventilation, artificial heart, aortic balloon pumping, blood oxygenators, heart-lung machines and are able to apply total parenteral nutrition in the patient with short bowel syndrome. However, the patient with acute liver failure (ALF) is still a major challenge[1].

ALF is a devastating clinical syndrome with a high mortality (60%-80%, depending on the cause and the experience of the clinical centre) with most frequent causes of death being brain edema, SIRS (systemic inflammatory response syndrome) and multiple organ failure (MOF). Emergency whole or partial liver transplantation (orthotopic (OLT) or auxiliary) is the only life-saving therapy.

Many attempts have been made to develop artificial liver support devices (ALSD): non-biological ones such as hemodialysis, charcoal hemoperfusion, selective plasma filtration, plasma exchange, hemo-diadsorption, albumin dialysis and biological ones such as whole liver perfusion, liver cell transplantation and bioartificial liver support.

The status of ALSDs has been the subject of many reviews, at least one a year, since 2001[2-14]. It does not seem wise to repeat their contents in this editorial and the reader is referred to the publications for global and/or detailed information. From reading them, at least one common conclusion emerges: devices that only support the failing detoxification function of the severely diseased liver are not sufficient to save the lives of ALF patients. It is generally accepted that the syndrome of ALF is not only determined by failing hepatic detoxification, but also by failing hepatic synthetic and regulatory function. This is also one of the conclusions of a workshop on ALF held in the USA in 2008[1].

The purpose of this editorial is, however, to analyze the critical issues that have to be solved in the near future.

CRITICAL ISSUES

What can we expect from cell or even organ-based ALSDs?

Whole animal liver perfusion as an ALSD seems to be a logic approach. There is some experience in a few case reports[15], but it has never been accepted as a common treatment, because of its complexity and its important xenotransplantation-related problems.

There are a few case reports concerning the more simple technique of liver cell transplantation (LCTX)[16] as a treatment for ALF. LCTX has at least 2 important drawbacks: (1) the availability of sufficient amounts of fully differentiated human liver cells; (2) the so far unsolved problem of transplanting large amounts (at least 10% of the normal parenchymal mass) of cells where there is adequate blood supply.

Ideally, a tissue-engineered transplantable liver should be the final solution. Such a bioengineered liver (BEL) should resemble the native liver as much as possible. This means a composite of parenchymal and non-parenchymal liver cells in a sponge-like configuration in which a vascular system provides, by direct plasma contact, oxygen and nutrients to the liver cells and which is equipped with a biliary outflow system. Ideally this BEL has to be connected to the splanchnic circulation (inflow tract), the caval vein system (outflow tract) and the intestine (biliary tract).

At present, such a BEL is only in a very preliminary and experimental phase[17-22] and, as second best to liver transplantation, patients have to be treated by one of the existing bioartificial livers (BALs) that can only be connected outside the body to the patient's systemic blood circulation

A BAL is defined as a bioreactor charged with liver cells that is connected outside the body to the blood or plasma circulation of the patient. Since a BAL supports both the failing detoxification and the failing synthetic and regulatory function of the diseased liver, it should have a beneficial effect on the degree of hepatic coma and the severity of MOF and, last but not least, on survival of ALF patients and preferably also of patients with acute on chronic liver disease (AoCLD).

In general, 4 types of BAL bioreactors can be distinguished: hollow fiber; flat plate and monolayer; perfused beds/scaffolds; encapsulation/suspension. Every system has its pros and cons. For details see Allen *et al*[2].

To prove their right to belong to the standard equipment of an intensive care unit BALs need to be validated in randomized, controlled clinical trials. Several questions have arisen as to whether pre-clinical research on BALs has been sufficient to justify their clinical application.

How good are results in experimental animals?

In general, the answer is positive. In many different models of ALF several BALs based on animal liver cells have shown to prolong survival significantly in comparison to standard treatment[23-33].

Can it contain a sufficient mass of parenchymal liver cells?

It is generally accepted (based on safe surgical resections) that survival is possible with a minimum of 20% of liver mass with optimal functionality. Assuming that the ALF patient still has some residual functioning liver mass, a BAL should contain at least 15% of liver mass. However, the reality is that isolated liver cells in a bioreactor do not have optimal functionality, so more than 15% (preferably 20%-30%) of liver mass will be required[34].

Furthermore, it is well known that parenchymal liver cells function at best in a 3-dimensional (3D) configuration. In addition their functionality increases when they are co-cultured with non-parenchymal cells[35] For these reasons, the ideal BAL should contain at least a mixture of well-differentiated liver cells in a 3D configuration at a mass of at least 20% of the normal liver (200 g cells in 1 kg of liver). Vital Therapies ELAD® (Extracorporeal Liver Assist Device) and Hep-Art AMC-BAL have this capacity.

How is bi-directional mass transport of oxygen, carbon dioxide, nutrients and liver cell products best guaranteed?

In BAL devices, bi-directional mass transfer is needed to provide nutrients to sustain cell viability and allow export of therapeutic cell products. Although most device designs address this, there are important limitations involving the use of semi-permeable membranes as a barrier between plasma and the bio-component. Bioreactors in which direct contact between plasma and the liver cells is guaranteed or those using semi-permeable membranes with high porosity are preferred.

In addition, liver cells need sufficient oxygen supply to function optimally[36]. The amount of oxygen actually dissolved in plasma is insufficient in this respect. Therefore, the cells in the bioreactor should see either full blood (with many problems such as hemolysis, clotting and platelet loss) or plasma with an extra oxygen carrier such as fluorocarbons[37] or locally supplied oxygen by oxygen capillaries interwoven with the cell containing hollow fibers (Modular Extracorporeal Liver Support)[38] or matrix (AMC-BAL)[39] inside the BAL: a so-called internal oxygenator.

Do BALs support drainage of bile?

Another aspect of current BALS is the universal absence of functional biliary excretion into an isolated compartment. Liver cells in 3D configuration can form functional canaliculi, but it is unknown to what extent biliary compounds still accumulate intracellularly and whether these will shorten the vitality of the cells. If some export of biliary compounds occurs at the basal lateral side to the plasma compartment a hybrid system removing them from this compartment is a logic next step. This might mean a modular system in which a BAL is combined with an artificial liver support device such as hemodialysis, charcoal hemoperfusion or albumin dialysis[40].

Table 1 BALs to be commercialized

Company	Device	Characteristics	Clinical experience & future plans
HepaLife	Hepa-Mate™ (previously HepatAssist)	Cryopreserved porcine cells, treatment 3-6 h for 1-5 d, charcoal column, and centrifugal plasmapheresis. Cell mass previously 60 g, in future trial 160 g	Phase Ⅱ/Ⅲ with HepatAssist in 171 ALF patients, only 9% improvement in OLT/NR as compared to controls. New trial in preparation
Vital therapies	ELAD®	Two-chambered hollow fiber cartridge with immortalized human C3A cell line. Treatment up to 10 d. Ultrafiltrate perfusion. 4 replaceable cartridges. Cell mass 4 g × 200 g	Controlled study with 25 ALF patients completed. 92% recovery OLT/NR. Controlled clinical trial in 49 AoCLD patients in China
Beijing and Nanjing Universities	TECA-BALSS/HBAL	Porcine cells (10-20 billion cells), outside compartment of hollow fiber devices	Phase I, 15 patients ALF and 3 patients AoCLD
Hep-Art	AMC-BAL	Perfused scaffold, oxygenation *in situ*, 10-15 billion freshly isolated SPF porcine hepatocytes	Phase Ⅰ/Ⅱa; 14 ALF patients. Safe, no PERV transmission

BAL: Biological artificial liver; ALF: Acute liver failure; OLT: Orthotopic liver transplant; AoCLD: Acute on chronic liver disease; PERV: Porcine endogenous retrovirus; NR: Native recovery; SPF: Specified pathogen-free; ELAD®: Extracorporeal Liver Assist Device; BALSS: Bioartificial Liver Support Systems; HBAL: Hybrid Bioartificial Liver; AMC-BAL: Academic Medical Center University of Amsterdam-Bioartificial Liver.

How long do cells remain viable and functional?

Cell viability is of paramount importance for the life supporting capacity of a BAL. The experience is that primary liver cells in a bioreactor lose functionality over time. With this already being the case under optimal culture conditions, it is especially problematic when the environment of cells is 100% human plasma. A decrease in function is even more marked if cells have to live in the plasma of ALF patients[41-46]. Increased concentrations of toxic products and probably decreased concentrations of essential nutrients play a role in this regard. For this reason, BALs are only temporarily sufficiently functional and have probably to be replaced after a critical time by fresh ones.

Which cells can be used in the BAL?

Freshly isolated or cryopreserved porcine liver cells or a human hepatoma cell line have been most frequently used as the biocomponent in clinically applied bioartificial livers.

Because of the xenotransplantation-related disadvantages of porcine cells (immunological reactions and possible pig endogenous retrovirus transmission)[47-50] and the shortage of primary human hepatocytes, a well-differentiated human liver cell line seems to be the Holy Grail. Such a cell line will have minimal immunogenicity, no risk of xenozoonosis and required functionality and availability.

Primary sources for the development of such human cell lines are human liver tumor derived cell lines, immortalized fetal or adult hepatocytes and stem cells of hepatic, hematopoietic, mesenchymal or embryonic origin. However, in all cell types tested so far, the *in vitro* differentiation cannot be stimulated to such an extent that functionality reaches that of primary human hepatocytes. The future lies in having more insight into differentiation-promoting factors and the influence of matrix and co-culture conditions on the functionality of liver cell lines[51].

What is the current situation?

A few BAL systems are currently in the process of being commercialized (Table 1).

Vital Therapies just finished a controlled clinical trial in 49 AoCLD patients in China. At its website (www.Vitaltherapies.com) one can read: "The pivotal China trial enrolled 49 patients and was carried out to support the registration of ELAD in China. It demonstrated statistically significant improvement in transplant free survival for acute-on-chronic liver failure patients treated with ELAD compared to the control group. These were mostly hepatitis B patients. VTI filed an application for marketing approval with the China SFDA in September 2007 and this application remains under review. These results remain to be confirmed in studies outside China".

HepaLife (www.hepalife.com) is promoting the Demetriou system (formerly brought by Circe and Arbios) that is based on cryopreserved porcine liver cells combined with a charcoal column connected to a plasmapheresis circuit. More than 200 patients have been treated by this system. In a multicenter controlled clinical trial in 181 ALF patients, time to death was significantly prolonged only in a subgroup of 83 patients with ALF of known etiology.

The Chinese ALSDs (TECA BALSS and HBAL) and the Dutch AMC-BAL have been tested in Phase 1-2a trials but are not yet commercially available.

Why is clinical proof of efficacy rather limited?

There are a few explanations: (1) The hardware used for bioreactors has not always been optimal. Hollow fiber-based bioreactors will have mass transfer restrictions and the absence of an internal oxygenator will limit cell functionality if plasma perfusion is the approach to the patient's blood circulation. In addition not all BALs have a 3D configuration of the liver cells. (2) The optimal human liver cell line is still not available. Hepatoma-derived cell lines are not fully differentiated, nor are immortalized liver cell lines. Future developments in this regard are urgently needed. (3) In the already published clinical trials, patient populations have been rather diverse making intention-to-treat analyses disappointing. (4) If BAL treatment is applied in ALF patients to bridge the waiting time for OLT, post-transplantation survival is not only dependent on BAL treatment but also on OLT.

CONCLUSION

Taking all these considerations together there is certainly a future for the BAL, based on pre-clinical data and the lessons that have been drawn from the existing controlled trials. A well-differentiated human liver cell line is still the Holy Grail. If this cell line were available, future clinical trials should be done with it in a BAL consisting of minimal mass transfer restrictions and equipped with cell oxygenation *in situ*, loaded with a sufficient 3D mass. Eventually it should be combined with albumin dialysis and refreshed after a critical time. The trial population should be as homogeneous as possible and well defined with regard to survival capacity.

POSSIBLE CONFLICT OF INTEREST

Chamuleau RAFM is CSO of Hep-Art Medical Devices B.V. that produces the AMC-BAL.

REFERENCES

1 **Lee WM**, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: Summary of a workshop. *Hepatology* 2008; **47**: 1401-1415
2 **Allen JW**, Hassanein T, Bhatia SN. Advances in bioartificial liver devices. *Hepatology* 2001; **34**: 447-455
3 **Hayes PC**, Lee A. What progress with artificial livers? *Lancet* 2001; **358**: 1286-1287
4 **Strain AJ**, Neuberger JM. A bioartificial liver--state of the art. *Science* 2002; **295**: 1005-1009
5 **Planchamp C**, Vu TL, Mayer JM, Reist M, Testa B. Hepatocyte hollow-fibre bioreactors: design, set-up, validation and applications. *J Pharm Pharmacol* 2003; **55**: 1181-1198
6 **van de Kerkhove MP**, Hoekstra R, Chamuleau RA, van Gulik TM. Clinical application of bioartificial liver support systems. *Ann Surg* 2004; **240**: 216-230
7 **Wigg AJ**, Padbury RT. Liver support systems: promise and reality. *J Gastroenterol Hepatol* 2005; **20**: 1807-1816
8 **Park JK**, Lee DH. Bioartificial liver systems: current status and future perspective. *J Biosci Bioeng* 2005; **99**: 311-319
9 **Rozga J**. Liver support technology--an update. *Xenotransplantation* 2006; **13**: 380-389
10 **O'Grady J**. Personal view: current role of artificial liver support devices. *Aliment Pharmacol Ther* 2006; **23**: 1549-1557
11 **Santoro A**, Mancini E, Ferramosca E, Faenza S. Liver support systems. *Contrib Nephrol* 2007; **156**: 396-404
12 **Stadlbauer V**, Jalan R. Acute liver failure: liver support therapies. *Curr Opin Crit Care* 2007; **13**: 215-221
13 **Phua J**, Lee KH. Liver support devices. *Curr Opin Crit Care* 2008; **14**: 208-215
14 **Sgroi A**, Serre-Beinier V, Morel P, Bühler L. What clinical alternatives to whole liver transplantation? Current status of artificial devices and hepatocyte transplantation. *Transplantation* 2009; **87**: 457-466
15 **Abouna GM**, Ganguly P, Jabur S, Tweed W, Hamdy H, Costa G, Farid E, Sater A. Successful ex vivo liver perfusion system for hepatic failure pending liver regeneration or liver transplantation. *Transplant Proc* 2001; **33**: 1962-1964
16 **Galvão FH**, de Andrade Júnior DR, de Andrade DR, Martins BC, Marson AG, Bernard CV, Dos Santos SA, Bacchella T, Machado MC. Hepatocyte transplantation: State of the art. *Hepatol Res* 2006; **36**: 237-247
17 **Chan C**, Berthiaume F, Nath BD, Tilles AW, Toner M, Yarmush ML. Hepatic tissue engineering for adjunct and temporary liver support: critical technologies. *Liver Transpl* 2004; **10**: 1331-1342
18 **Diekmann S**, Bader A, Schmitmeier S. Present and Future Developments in Hepatic Tissue Engineering for Liver Support Systems : State of the art and future developments of hepatic cell culture techniques for the use in liver support systems. *Cytotechnology* 2006; **50**: 163-179
19 **Fiegel HC**, Kaufmann PM, Bruns H, Kluth D, Horch RE, Vacanti JP, Kneser U. Hepatic tissue engineering: from transplantation to customized cell-based liver directed therapies from the laboratory. *J Cell Mol Med* 2008; **12**: 56-66
20 **Ishii Y**, Saito R, Marushima H, Ito R, Sakamoto T, Yanaga K. Hepatic reconstruction from fetal porcine liver cells using a radial flow bioreactor. *World J Gastroenterol* 2008; **14**: 2740-2747
21 **Linke K**, Schanz J, Hansmann J, Walles T, Brunner H, Mertsching H. Engineered liver-like tissue on a capillarized matrix for applied research. *Tissue Eng* 2007; **13**: 2699-2707
22 **Sarkis R**, Wen L, Honiger J, Baudrimont M, Delelo R, Calmus Y, Capeau J, Nordlinger B. [Intraperitoneal transplantation of isolated hepatocytes of the pig: the implantable bioartificial liver] *Chirurgie* 1998; **123**: 41-46
23 **Flendrig LM**, Calise F, Di Florio E, Mancini A, Ceriello A, Santaniello W, Mezza E, Sicoli F, Belleza G, Bracco A, Cozzolino S, Scala D, Mazzone M, Fattore M, Gonzales E, Chamuleau RA. Significantly improved survival time in pigs with complete liver ischemia treated with a novel bioartificial liver. *Int J Artif Organs* 1999; **22**: 701-709
24 **Abrahamse SL**, van de Kerkhove MP, Sosef MN, Hartman R, Chamuleau RA, van Gulik TM. Treatment of acute liver failure in pigs reduces hepatocyte function in a bioartificial liver support system. *Int J Artif Organs* 2002; **25**: 966-974
25 **Enosawa S**, Miyashita T, Saito T, Omasa T, Matsumura T. The significant improvement of survival times and pathological parameters by bioartificial liver with recombinant HepG2 in porcine liver failure model. *Cell Transplant* 2006; **15**: 873-880
26 **Flendrig LM**, Chamuleau RA, Maas MA, Daalhuisen J, Hasset B, Kilty CG, Doyle S, Ladiges NC, Jörning GG, la Soe JW, Sommeijer D, te Velde AA. Evaluation of a novel bioartificial liver in rats with complete liver ischemia: treatment efficacy and species-specific alpha-GST detection to monitor hepatocyte viability. *J Hepatol* 1999; **30**: 311-320
27 **Hochleitner B**, Hengster P, Bucher H, Ladurner R, Schneeberger S, Krismer A, Kleinsasser A, Barnas U, Klima G, Margreiter R. Significant survival prolongation in pigs with fulminant hepatic failure treated with a novel microgravity-based bioartificial liver. *Artif Organs* 2006; **30**: 906-914
28 **Kamohara Y**, Fujioka H, Eguchi S, Kawashita Y, Furui J, Kanematsu T. Comparative study of bioartificial liver support and plasma exchange for treatment of pigs with fulminant hepatic failure. *Artif Organs* 2000; **24**: 265-270
29 **Kawazoe Y**, Eguchi S, Sugiyama N, Kamohara Y, Fujioka H, Kanematsu T. Comparison between bioartificial and artificial liver for the treatment of acute liver failure in pigs. *World J Gastroenterol* 2006; **12**: 7503-7507
30 **Khalili TM**, Navarro A, Ting P, Kamohara Y, Arkadopoulos N, Solomon BA, Demetriou AA, Rozga J. Bioartificial liver treatment prolongs survival and lowers intracranial pressure in pigs with fulminant hepatic failure. *Artif Organs* 2001; **25**: 566-570
31 **Sheil AG**, Sun J, Mears DC, Waring M, Woodman K, Johnston B, Horvat M, Watson KJ, Koutalistras N, Wang LS. Preclinical trial of a bioartificial liver support system in a porcine fulminant hepatic failure model. *Aust N Z J Surg* 1996; **66**: 547-552
32 **Sosef MN**, Abrahamse LS, van de Kerkhove MP, Hartman R, Chamuleau RA, van Gulik TM. Assessment of the AMC-bioartificial liver in the anhepatic pig. *Transplantation* 2002; **73**: 204-209
33 **Tréhout D**, Desille M, Doan BT, Mahler S, Frémond B, Mallédant Y, Campion JP, Desbois J, Beloeil JC, de Certaines J, Clément B. Follow-up by one- and two-dimensional NMR

of plasma from pigs with ischemia-induced acute liver failure treated with a bioartificial liver. *NMR Biomed* 2002; **15**: 393-403

34 **Morsiani E**, Brogli M, Galavotti D, Pazzi P, Puviani AC, Azzena GF. Biologic liver support: optimal cell source and mass. *Int J Artif Organs* 2002; **25**: 985-993

35 **Kidambi S**, Yarmush RS, Novik E, Chao P, Yarmush ML, Nahmias Y. Oxygen-mediated enhancement of primary hepatocyte metabolism, functional polarization, gene expression, and drug clearance. *Proc Natl Acad Sci USA* 2009; **106**: 15714-15719

36 **Catapano G**, De BL. Combined effect of oxygen and ammonia on the kinetics of ammonia elimination and oxygen consumption of adherent rat liver cells. *Int J Artif Organs* 2002; **25**: 151-157

37 **Nieuwoudt M**, Engelbrecht GH, Sentle L, Auer R, Kahn D, van der Merwe SW. Non-toxicity of IV injected perfluorocarbon oxygen carrier in an animal model of liver regeneration following surgical injury. *Artif Cells Blood Substit Immobil Biotechnol* 2009; **37**: 117-124

38 **Gerlach JC**, Lemmens P, Schön M, Janke J, Rossaint R, Busse B, Puhl G, Neuhaus P. Experimental evaluation of a hybrid liver support system. *Transplant Proc* 1997; **29**: 852

39 **Flendrig LM**, la Soe JW, Jörning GG, Steenbeek A, Karlsen OT, Bovée WM, Ladiges NC, te Velde AA, Chamuleau RA. In vitro evaluation of a novel bioreactor based on an integral oxygenator and a spirally wound nonwoven polyester matrix for hepatocyte culture as small aggregates. *J Hepatol* 1997; **26**: 1379-1392

40 **Sauer IM**, Zeilinger K, Pless G, Kardassis D, Theruvath T, Pascher A, Goetz M, Neuhaus P, Gerlach JC. Extracorporeal liver support based on primary human liver cells and albumin dialysis--treatment of a patient with primary graft non-function. *J Hepatol* 2003; **39**: 649-653

41 **Newsome PN**, Tsiaoussis J, Ansell I, Ross JA, Sethi T, Hayes PC, Plevris JN. Acute liver failure serum reduces hepatocyte-matrix adhesion by a cell death-independent mechanism. *J Hepatol* 2001; **34** Suppl 1: 29

42 **Anderson C**, Thabrew MI, Hughes RD. Assay to detect inhibitory substances in serum of patients with acute liver failure. *Int J Artif Organs* 1999; **22**: 113-117

43 **Newsome PN**, Tsiaoussis J, Masson S, Buttery R, Livingston C, Ansell I, Ross JA, Sethi T, Hayes PC, Plevris JN. Serum from patients with fulminant hepatic failure causes hepatocyte detachment and apoptosis by a beta(1)-integrin pathway. *Hepatology* 2004; **40**: 636-645

44 **Hughes RD**, Yamada H, Gove CD, Williams R. Inhibitors of hepatic DNA synthesis in fulminant hepatic failure. *Dig Dis Sci* 1991; **36**: 816-819

45 **Mitry RR**, Hughes RD, Bansal S, Lehec SC, Wendon JA, Dhawan A. Effects of serum from patients with acute liver failure due to paracetamol overdose on human hepatocytes in vitro. *Transplant Proc* 2005; **37**: 2391-2394

46 **Saich R**, Selden C, Rees M, Hodgson H. Characterization of pro-apoptotic effect of liver failure plasma on primary human hepatocytes and its modulation by molecular adsorbent recirculation system therapy. *Artif Organs* 2007; **31**: 732-742

47 **Lee JH**, Moran C. Current status of xenotransplantation - A review. *Asian Australas J Anim Sci* 2001; **14**: 1497-1504

48 **Patience C**, Patton GS, Takeuchi Y, Weiss RA, McClure MO, Rydberg L, Breimer ME. No evidence of pig DNA or retroviral infection in patients with short-term extracorporeal connection to pig kidneys. *Lancet* 1998; **352**: 699-701

49 **Wang HH**, Wang YJ, Liu HL, Liu J, Huang YP, Guo HT, Wang YM. Detection of PERV by polymerase chain reaction and its safety in bioartificial liver support system. *World J Gastroenterol* 2006; **12**: 1287-1291

50 **Xu H**, Sharma A, Okabe J, Cui C, Huang L, Wei YY, Wan H, Lei Y, Logan JS, Levy MF, Byrne GW. Serologic analysis of anti-porcine endogenous retroviruses immune responses in humans after ex vivo transgenic pig liver perfusion. *ASAIO J* 2003; **49**: 407-416

51 **Chamuleau RA**, Deurholt T, Hoekstra R. Which are the right cells to be used in a bioartificial liver? *Metab Brain Dis* 2005; **20**: 327-335

S- Editor Li LF **L- Editor** Cant MR **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.26

World J Gastrointest Surg 2009 November 30; 1(1): 26-29
ISSN 1948-9366 (online)

GUIDELINES FOR CLINICAL PRACTICE

Surgery for gallbladder cancer: The need to generate greater evidence

Shailesh V Shrikhande, Savio G Barreto

Shailesh V Shrikhande, Department of Gastrointestinal Surgical Oncology, Tata Memorial Hospital, Mumbai 400012, India
Savio G Barreto, Department of General and Digestive Surgery, Flinders Medical Centre, Adelaide 5042, Australia
Author contributions: Shrikhande SV conceived and designed the review, revised it critically and approved the final edition; Barreto SG acquired the data, drafted the article, analysis and interpretation of data, and approved the final version.
Correspondence to: Shailesh V Shrikhande, MBBS, MS, MD, Associate Professor and Consultant Surgeon, Department of Gastrointestinal Surgical Oncology, Tata Memorial Hospital, Mumbai 400012, India. shailushrikhande@hotmail.com
Telephone: +91-22-24177173 Fax: +91-22-24148114
Received: October 9, 2009 Revised: October 30, 2009
Accepted: November 6, 2009
Published online: November 30, 2009

Abstract

The outcomes for gallbladder cancer remain largely dismal to this day. Overall, the low incidence of gallbladder cancer around the world coupled with an even lower number of patients amenable to surgery at the time of presentation, has precluded the generation of evidence-based guidelines for the management of this cancer. However, while the incidence of the cancer may be decreasing in some parts of the world, in other countries such as India, Japan and Chile, gallbladder cancer continues to affect a sizeable population of patients. As such, there is a growing need to define what constitutes an adequate surgery for each stage of this cancer, based on sound evidence. This editorial provides a broad overview of the existing problems in the management of gallbladder cancer and appeals for multi-institutional studies aimed at answering some of the pertinent questions on the surgical management of gallbladder cancer.

Key words: Treatment outcome; Lymphadenectomy; Incidence; Survival rate

Peer reviewer: Eddie K Abdalla, MD, Associate Professor, The University of Texas M. D. Anderson Cancer Center, PO Box 301402, Houston, TX 77230-1402, United States

Shrikhande SV, Barreto SG. Surgery for gallbladder cancer: The need to generate greater evidence. *World J Gastrointest Surg* 2009; 1(1): 26-29 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/26.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.26

INTRODUCTION

It is indeed despairing to read articles on gallbladder cancer outcomes which always begin with the reference to the disease as one that is associated with a dismal prognosis. Surgery remains the only treatment modality associated with a benefit in terms of survival[1] in gallbladder cancer. However, what is most disconcerting is the lack of consensus across the world on what constitutes an optimal operation for a given stage of the disease. Many of the surgical concepts in gallbladder cancer are based on what "we think" as appropriate. The confusion is aptly summed up by the paper by Sasaki *et al*[1] in which 16 different resections had been performed. The cause for all this uncertainty stems from the fact that this disease is relatively uncommon around the world and so hardly any (if at all) of the approaches have been evaluated in an evidence-based manner. Another confounding factor is the difference in the etiology and pathogenesis of the disease in Japan (from where most of the reported data on surgical management of gallbladder cancer arises) and the rest of the world[2]. This brings us to the question of whether we can draw conclusions from the existing literature that can aid us in deciding the correct surgery.

CURRENT SURGICAL PRACTICE

T1 stage

Most surgeons would agree that for a tumor that is T1a by the TNM classification[3], a simple cholecystectomy constitutes an adequate surgery. However, the view on T1b tumors is not so clear. While some authors have suggested that a simple cholecystectomy is sufficient in such patients[4,5], we[6] and others[7], have found evidence of lymph node metastases in these patients as well as disease in the gallbladder fossa (even up to 35%)[5,6]. This seems to indicate that performing a lymphadenectomy with excision of at least a wedge of liver tissue from segments 4b and 5 seems to be prudent[8], the benefit of which needs to be studied in prospective randomized studies.

T2-4

In the case of tumors that are T2-4, the basic principles of resection include a cholecystectomy with an *en bloc* resection of the liver, with a lymphadenectomy with or without a radical resection of the bile duct[7]. The extent of liver tissue to be resected continues to be a matter of conjecture. Some surgeons routinely prescribe major hepatic resections for all stages of gallbladder cancer[9-11]. However, there is growing evidence that major hepatic resections are associated with an increased morbidity (intra-abdominal abscesses, bilomas, hepatic failure) and even mortality[11-13]. Even here, there is increasing evidence that major resections may be devoid of any survival benefit[9,14,15] as compared to 2-3 cm wedge resections of segment IVb and V.

ROLE OF LYMPHADENECTOMY

In most solid organ cancers, including gastric and colorectal cancers, lymphadenectomy provides important staging information and it may also be associated with a reduction in local recurrence. In gallbladder cancers, while most surgeons perform a standard regional lymphadenectomy (which includes lymph nodes around the cystic duct, pericholedochal and hepatoduodenal ligaments), some surgeons recommend an extended resection to include retroportal, posterosuperior pancreaticoduodenal, posteroinferior pancreaticoduodenal, common hepatic artery, celiac, superior mesenteric and interaorticocaval lymph nodes for tumors that are stage Ⅲ and Ⅳ[16]. However, the benefit of such an exercise in improving overall survival remains contentious[17,18]. In addition, attempts should perhaps be made to define a minimum number of lymph nodes (from specific locations) necessary for optimal staging (and perhaps prognostication) of gall bladder cancer.

EXTRAHEPATIC BILE DUCT RESECTION

Japanese surgeons have long since recommended the routine excision of the extra-hepatic bile duct in all stages of gallbladder cancer[19-21]. The rationale behind this is that in the early stages of the disease, excision of the bile duct would aid clearance of lymph nodes and occult cancer cells along the hepatoduodenal ligament and in the connective tissue[22]. In the advanced stages, it was intended to address the issue of perineural invasion[23]. However, while some Japanese surgeons have demonstrated a benefit in terms of overall survival[24-26], others have failed to do so[27-29]. Moreover, numerous studies have highlighted the increased morbidity associated with routine excision of the duct[27,28,30]. However, despite all this controversy, there do exist specific indications where the extrahepatic duct may have to be excised and these include a positive cystic duct margin, presence of an anomalous bile duct junction, and synchronous malignancy in the extrahepatic bile duct, as well as to aid lymph nodal clearance when there are large lymph nodes, the clearance of which may be associated with a risk of devascularizing the common bile duct.

PORT-SITE METASTASES

With the increasing use of laparoscopic cholecystectomy, there will always be a risk of port-site metastases. Again the management of port-site metastases in patients who are undergoing radical resection for incidental gallbladder cancers seems to be contentious. While, Giuliante *et al*[31] recommended routine "complete" excision of the port sites, surgically this may not always be feasible. More importantly, there is no evidence to date to indicate that routine excision of the port sites improves overall survival.

PATIENTS WITH METASTATIC DISEASE

In patients with stage Ⅳ disease, there remain proponents of radical surgery[25,32,33] even in stage Ⅳ disease. However, prior to interpreting these results it must be understood that patients with stage Ⅳa and even b need not have distant metastases. Thus the survival advantage that has been demonstrated[32,33] is primarily in those patients without liver, peritoneal or distant metastases. More robust data is needed to determine whether there exists a survival benefit of radical resections in these patients or, for that matter, even in patients with liver metastases (anecdotal reports exist on the benefit of radical surgery in these patients).

FUTURE PERSPECTIVES

With a reported decline in the incidence of gallbladder cancer (based on the surrogate marker of gallbladder cancer mortality) in the United States, Australasia and most parts of Europe[34], it appears that the drive to generate more evidence on the appropriate surgery for the cancer must come from countries with a higher incidence of the disease.

Pertinent aspects that need to be answered in the management of gallbladder cancer include: (1) consensus definitions of the various surgeries to be performed for

gallbladder cancer. There has been a considerable overlap and interchangeable use of terms when defining the surgery performed in gallbladder cancer including extended cholecystectomy and radical cholecystectomy[35]; (2) the role of radical cholecystectomy in T1b disease; (3) the role of extrahepatic bile duct resection in the various stages of the disease; (4) the extent of liver/gallbladder bed to be resected for each stage of the disease; (5) the extent of lymphadenectomy for the different stages of the disease. The latter aspects can probably be best answered by randomized controlled trials which would need a large number of patients to be enrolled in multicenter studies. Such a task would require a large collaborative effort from institutions in high incidence areas around the world.

CONCLUSION

We should accept the fact that gallbladder cancer is a disease with low numbers of patients amenable to surgery. Thus, instead of retrospectively analyzing individual institutional data, high volume institutions with the necessary expertise for treating gallbladder cancer should collaborate with a view to generating strong evidence to support the different surgical strategies - a move that may provide us with the evidence-based surgical guidelines we are looking for to better enable us to tackle this dreadful disease.

REFERENCES

1 **Sasaki R**, Itabashi H, Fujita T, Takeda Y, Hoshikawa K, Takahashi M, Funato O, Nitta H, Kanno S, Saito K. Significance of extensive surgery including resection of the pancreas head for the treatment of gallbladder cancer--from the perspective of mode of lymph node involvement and surgical outcome. *World J Surg* 2006; **30**: 36-42

2 **Shukla PJ**, Barreto SG, Gupta P, Neve R, Ramadwar M, Deodhar K, Mehta S, Shrikhande SV, Mohandas KM. Is there a role for estrogen and progesterone receptors in gall bladder cancer? *HPB* (Oxford) 2007; **9**: 285-288

3 **Gallbladder**. American Joint Committee on Cancer: AJCC Cancer staging manual. 5th ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1997: 103-108

4 **Wakai T**, Shirai Y, Yokoyama N, Nagakura S, Watanabe H, Hatakeyama K. Early gallbladder carcinoma does not warrant radical resection. *Br J Surg* 2001; **88**: 675-678

5 **de Aretxabala X**, Roa I, Hepp J, Maluenda F, Mordojovich G, Leon J, Roa JC. Early gallbladder cancer: Is further treatment necessary? *J Surg Oncol* 2009; **100**: 589-593

6 **Shukla PJ**, Barreto G, Kakade A, Shrikhande SV. Revision surgery for incidental gallbladder cancer: factors influencing operability and further evidence for T1b tumours. *HPB* (Oxford) 2008; **10**: 43-47

7 **Ogura Y**, Mizumoto R, Isaji S, Kusuda T, Matsuda S, Tabata M. Radical operations for carcinoma of the gallbladder: present status in Japan. *World J Surg* 1991; **15**: 337-343

8 **Shukla PJ**, Barreto SG. Gallbladder cancer: we need to do better! *Ann Surg Oncol* 2009; **16**: 2084-2085

9 **Reddy SK**, Marroquin CE, Kuo PC, Pappas TN, Clary BM. Extended hepatic resection for gallbladder cancer. *Am J Surg* 2007; **194**: 355-361

10 **Pack GT**, Miller TR, Brasfield RD. Total right hepatic lobectomy for cancer of the gallbladder; report of three cases. *Ann Surg* 1955; **142**: 6-16

11 **Kondo S**, Nimura Y, Hayakawa N, Kamiya J, Nagino M, Uesaka K. Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. *Br J Surg* 2000; **87**: 418-422

12 **Todoroki T**, Kawamoto T, Takahashi H, Takada Y, Koike N, Otsuka M, Fukao K. Treatment of gallbladder cancer by radical resection. *Br J Surg* 1999; **86**: 622-627

13 **Dixon E**, Vollmer CM Jr, Sahajpal A, Cattral M, Grant D, Doig C, Hemming A, Taylor B, Langer B, Greig P, Gallinger S. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. *Ann Surg* 2005; **241**: 385-394

14 **D'Angelica M**, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009; **16**: 806-816

15 **Yoshikawa T**, Araida T, Azuma T, Takasaki K. Bisubsegmental liver resection for gallbladder cancer. *Hepatogastroenterology* 1998; **45**: 14-19

16 **Wang JD**, Liu YB, Quan ZW, Li SG, Wang XF, Shen J. Role of regional lymphadenectomy in different stage of gallbladder carcinoma. *Hepatogastroenterology* 2009; **56**: 593-596

17 **Bartlett DL**, Fong Y, Fortner JG, Brennan MF, Blumgart LH. Long-term results after resection for gallbladder cancer. Implications for staging and management. *Ann Surg* 1996; **224**: 639-646

18 **Benoist S**, Panis Y, Fagniez PL. Long-term results after curative resection for carcinoma of the gallbladder. French University Association for Surgical Research. *Am J Surg* 1998; **175**: 118-122

19 **Nakamura S**, Sakaguchi S, Suzuki S, Muro H. Aggressive surgery for carcinoma of the gallbladder. *Surgery* 1989; **106**: 467-473

20 **Matsumoto Y**, Fujii H, Aoyama H, Yamamoto M, Sugahara K, Suda K. Surgical treatment of primary carcinoma of the gallbladder based on the histologic analysis of 48 surgical specimens. *Am J Surg* 1992; **163**: 239-245

21 **Tsukada K**, Hatakeyama K, Kurosaki I, Uchida K, Shirai Y, Muto T, Yoshida K. Outcome of radical surgery for carcinoma of the gallbladder according to the TNM stage. *Surgery* 1996; **120**: 816-821

22 **Shimizu Y**, Ohtsuka M, Ito H, Kimura F, Shimizu H, Togawa A, Yoshidome H, Kato A, Miyazaki M. Should the extrahepatic bile duct be resected for locally advanced gallbladder cancer? *Surgery* 2004; **136**: 1012-1017; discussion 1018

23 **Sakamoto Y**, Kosuge T, Shimada K, Sano T, Hibi T, Yamamoto J, Takayama T, Makuuchi M. Clinical significance of extrahepatic bile duct resection for advanced gallbladder cancer. *J Surg Oncol* 2006; **94**: 298-306

24 **Suzuki S**, Yokoi Y, Kurachi K, Inaba K, Ota S, Azuma M, Konno H, Baba S, Nakamura S. Appraisal of surgical treatment for pT2 gallbladder carcinomas. *World J Surg* 2004; **28**: 160-165

25 **Kosuge T**, Sano K, Shimada K, Yamamoto J, Yamasaki S, Makuuchi M. Should the bile duct be preserved or removed in radical surgery for gallbladder cancer? *Hepatogastroenterology* 1999; **46**: 2133-2137

26 **Kaneoka Y**, Yamaguchi A, Isogai M, Harada T, Suzuki M. Hepatoduodenal ligament invasion by gallbladder carcinoma: histologic patterns and surgical recommendation. *World J Surg* 2003; **27**: 260-265

27 **Chijiiwa K**, Nakano K, Ueda J, Noshiro H, Nagai E, Yamaguchi K, Tanaka M. Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. *J Am Coll Surg* 2001; **192**: 600-607

28 **Shimada H**, Endo I, Togo S, Nakano A, Izumi T, Nakagawara G. The role of lymph node dissection in the treatment of gallbladder carcinoma. *Cancer* 1997; **79**: 892-899

29 **Kokudo N**, Makuuchi M, Natori T, Sakamoto Y, Yamamoto J, Seki M, Noie T, Sugawara Y, Imamura H, Asahara S, Ikari

T. Strategies for surgical treatment of gallbladder carcinoma based on information available before resection. *Arch Surg* 2003; **138**: 741-750; discussion 750

30 **Muratore A**, Polastri R, Bouzari H, Vergara V, Capussotti L. Radical surgery for gallbladder cancer: a worthwhile operation? *Eur J Surg Oncol* 2000; **26**: 160-163

31 **Giuliante F**, Ardito F, Vellone M, Clemente G, Nuzzo G. Port-sites excision for gallbladder cancer incidentally found after laparoscopic cholecystectomy. *Am J Surg* 2006; **191**: 114-116

32 **Shimizu H**, Kimura F, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Nozawa S, Furukawa K, Mitsuhashi N, Takeuchi D, Suda K, Yoshioka I, Miyazaki M. Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. *J Hepatobiliary Pancreat Surg* 2007; **14**: 358-365

33 **Chijiiwa K**, Kai M, Nagano M, Hiyoshi M, Ohuchida J, Kondo K. Outcome of radical surgery for stage IV gallbladder carcinoma. *J Hepatobiliary Pancreat Surg* 2007; **14**: 345-350

34 **Randi G**, Malvezzi M, Levi F, Ferlay J, Negri E, Franceschi S, La Vecchia C. Epidemiology of biliary tract cancers: an update. *Ann Oncol* 2009; **20**: 146-159

35 **Shukla PJ**, Barreto SG. Approach to carcinoma of the gallbladder. In: Gupta RL, ed. Recent Advances in Surgery 11. Indian ed. New Delhi: Jaypee Brothers, 2009: 188-207

S- Editor Li LF **L- Editor** Cant MR **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.30

World J Gastrointest Surg 2009 November 30; 1(1): 30-37
ISSN 1948-9366 (online)

REVIEW

Early response evaluation and prediction in neoadjuvant-treated patients with esophageal cancer

Joerg Theisen, Bernd Krause, Christian Peschel, Roland Schmid, Hans Geinitz, Helmut Friess

Joerg Theisen, Helmut Friess, Department of Surgery, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany
Bernd Krause, Department of Nuclear Medicine, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany
Christian Peschel, Department of Oncology, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany
Roland Schmid, Department of Gastroenterology, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany
Hans Geinitz, Department of Radiation Oncology, Klinikum rechts der Isar, TU Muenchen, 81675 Munich, Germany
Author contributions: Theisen J and Friess H designed the study, acquired and analyzed the data, drafted the article and approved the final version; Krause B, Peschel C, Schmid R and Geinitz H acquired and analyzed the data, drafted the article and approved the final version.
Correspondence to: Joerg Theisen, PhD, Department of Surgery, Klinikum rechts der Isar, TU Muenchen, Ismaninger Str. 22, D-81675 Munich,
Germany. theisen@chir.med.tu-muenchen.de
Telephone: +49-89-41405134 Fax: +49-98-41404870
Received: October 9, 2009 Revised: November 3, 2009
Accepted: November 10, 2009
Published online: November 30, 2009

Abstract

Since the introduction of multimodal therapy regimens, the prognosis of esophageal cancer has improved. There is undoubtedly true for patients with surgically resected tumors in the case of a response to neoadjuvant chemotherapy or chemoradiation. Important conclusions can be drawn from this regarding the indication for perioperative therapies, the radicality of surgery, or the surgical indications. Thus, most of the current research in this field is aimed at the early identification of this subset of patients, at the beginning of, or even before, neoadjuvant treatment. Conventional staging tools have failed to predict responses to neoadjuvant therapy. However, molecular imaging methods, e.g. positron emission tomography (PET)-scans, have shown promising results in the early selection of responders and non-responders during the course of neoadjuvant therapy, allowing physicians to alter the treatment plan accordingly. Even more desirable is the identification of potential responders before the start of neoadjuvant therapy. Preliminary molecular data on biopsy specimens demonstrate the possibility of early response prediction in these patients. We present the current knowledge on response evaluation and prediction in esophageal cancer and draw conclusions for future clinical practice and studies in this review.

Key words: Esophageal cancer; Response prediction; Individualized therapy

Peer reviewers: Giuseppe Aprile, MD, Department of Medical Oncology, University Hospital of Udine, Piazzale S Maria della Misericordia, 33100 Udine, Italy; Mehmet Fatih Can, MD, Kent Koop Mh. 11.Cad. Guneyce Merkez Sit. A/10, 06370, Batikent, Ankara, Turkey

Theisen J, Krause B, Peschel C, Schmid R, Geinitz H, Friess H. Early response evaluation and prediction in neoadjuvant-treated patients with esophageal cancer. *World J Gastrointest Surg* 2009; 1(1): 30-37 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/30.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.30

INTRODUCTION

The last decade has seen a change in the therapy of patients with esophageal cancer. For many years, the standard therapy for locally advanced lesions has been surgical resection. However, overall survival for patients with locally advanced tumors after resection remains poor, with a five-year survival rate between 10% and 30%[1,2]. Most patients still present with an advanced tumor stage; therefore, multimodal therapy regimens have been introduced, some using neoadjuvant chemotherapy or radiochemotherapy followed by radical resection, whereas others use adjuvant protocols[3]. Furthermore, trials have been presented in which surgery was omitted completely. Currently,

there is no evidence-based international agreement on one or the other multimodal approach. The results have been conflicting. Some have demonstrated a benefit for neoadjuvant radiochemotherapy, others for neoadjuvant chemotherapy, and some favour an adjuvant approach. Other published studies did not find any difference in survival for a multimodal concept. There are multiple reasons for these marginal differences and for the controversies in the preferred regimens, such as the heterogeneity of the groups analyzed, mixing squamous cell cancer of the esophagus with esophageal adenocarcinoma or analyzing true esophageal adenocarcinoma (Barrett's cancer) together with carcinomas of the esophago-gastric junction and proximal gastric carcinomas. It is very important to stress that esophageal adenocarcinoma and squamous cell cancer of the esophagus have to be considered as completely different entities and therefore separate analysis is mandatory[4]. Additionally several protocols for chemotherapy and radiochemotherapy have been used. However, careful analysis of the published results indicates that there is always a subset of patients benefiting from the multimodal approach[5]. These are patients who show a response to the respective neoadjuvant or adjuvant protocol. This is the case for all the different regimens applied. Unfortunately, in most studies the treatment response is not clearly defined. The current gold standard for response assessment is the pathohistological statement of the amount of viable tumor cells within the resected specimen. This gold standard might be an adequate tool for all adjuvant protocols because of the opportunity to tailor postresection therapy accordingly. However, the current trend favors neoadjuvant trials. The Patterns of Care studies in the US showed that neoadjuvant chemoradiation therapy increased from approximately 10% during 1992-1994 to approximately 26% in 1996-1999 for locally advanced esophageal carcinomas[5]. A meta-analysis of the survival benefit in the neoadjuvant setting found an increase in survival for neoadjuvant radiochemotherapy in squamous cell cancer of the esophagus and to a lesser extent for adenocarcinoma using chemotherapy alone. Protocols using radiochemotherapy in the neoadjuvant setting in patients with esophageal adenocarcinoma did show a benefit compared to chemotherapy alone[6]. For this preoperative approach, the pathohistological assessment of response is available too late to modify any preoperative protocols. Therefore, current research activities aim to identify predictors of response early or even before the neoadjuvant concepts are applied to individualize therapies according to the respective tumor behaviour.

There are several theoretical components available for the prediction of pretherapeutic response. Demographic data, initial staging imaging tools, biopsies, and serum. Pure clinical response evaluation after neoadjuvant therapy for esophageal cancer is highly inaccurate[7]. Despite numerous studies in this field, no clear reliable candidate marker predicting response was identified. However, recent studies using new technologies such as gene chips or molecular imaging have shown promising early results towards a response prediction or response evaluation.

Table 1 Histopathological response classification according to the amount of residual tumor within the tumor bed according to Becker *et al*[9]

Grade	Description	Response
1a	No residual tumor/tumor bed	Responder
1b	< 10% residual tumor/tumor bed	Responder
2	10%-50% residual tumor/tumor bed	Partial responder
3	> 50% residual tumor/tumor bed	Non-responder

HISTOPATHOLOGICAL RESPONSE

The current gold standard for response prediction is the histopathological assessment of the tumor regression grade as described by Mandard *et al*[8] and slightly modified by Becker *et al*[9] for esophageal and gastric tumors. This regression grading system stratifies response based on the biological effect of radiation or chemotherapy on the amount of remaining viable tumor cells. There are three to five grades based on the ratio of fibrosis to remaining viable tumor content. Complete pathohistological response means that there are no viable residual tumor cells present. Partial response is defined as the presence of tumor cells scattered through the fibrosis, and minimal regression showing residual cancer outgrowing fibrosis. Absence of any regressive changes is considered a no-change situation. For esophageal and gastric tumors, Becker *et al*[9] described a clinically useful four-grade classification based on an estimation of the percentage of vital tumor tissue in relation to the tumor bed (Table 1). Patients with no or < 10% residual tumor cells (tumor regression score 1) are classified as responders. All other tumors (tumor regression score 2: 10%-50% residual tumor cells and tumor regression score 3: > 50% residual tumor cells) were classified as non responders. This tumor response grading system is clearly associated with survival and currently serves as the gold standard for response assessment. However, this prognostic system is not available prior to neoadjuvant therapy and therefore is more useful in the potential adjuvant setting.

To date, a predictor of response based on demographics or conventional imaging information has not emerged. Performance status, primary location or age has not been shown to be associated with pathological response[10].

APPROACH TO RESPONSE ASSESSMENT

In addition to the availability of components such as serum or biopsies, several methods have been used to predict as early as possible the response to neoadjuvant therapy. In the past, most studies used immunohistochemical methods to assess the response. The approach to the analyzed proteins has been either chemotherapy drugs driven or proteins have been chosen that have been shown to play a role in the behaviour of certain malignancies. However, single potential biomarkers have failed to sufficiently predict response to neoadjuvant therapy. This is not surprising considering the complex interactions between all the gene products expressed by the cells, and the many proteins

involved in numerous cellular functions, such as apoptosis, DNA repair, and the metabolism and detoxification of drugs; all of which contribute to the individual response of a given tumor. Therefore, it is likely that multiple markers are needed to define the sensitivity or resistance of tumors to specific drugs. In recent years, new technologies using microarray gene chips or proteomics have been used for response prediction studies. These technologies enable the analysis of thousands of genes at the same time with a single biopsy specimen at the RNA/DNA or protein level.

Molecular imaging has emerged in recent years as an important technique. Many studies have been published showing a significant correlation of tumor metabolism and pathohistological response. Based on these results, therapy regimens have been successfully changed according to the response behaviour. Unfortunately, this information is not available prior to the therapy. At least two weeks of the neoadjuvant chemo - or radiochemotherapy has to be given before the molecular imaging is able to distinguish between responders and non-responders.

MOLECULAR RESPONSE PREDICTION IN ESOPHAGEAL SQUAMOUS CELL CANCER

Patients with locally advanced squamous cell cancer of the esophagus are currently treated with either neoadjuvant radiochemotherapy or definitive radiochemotherapy. These regimens differ in the radiation dosages used. In the neoadjuvant setting, approximately 45 Gray are administered followed by esophagectomy with lymphadenectomy. Radiochemotherapy without resection applies approximately 50 to 60 Gray to the tumor region and the corresponding lymph nodes areas.

In a retrospective study of 68 patients with locally advanced esophageal squamous cell cancer who received a multimodal treatment with 5-Fluorouracil (5-FU) based radiochemotherapy, Sarbia and colleagues examined the correlation of the presence of genetic polymorphisms in genes involved in folate metabolism with the response behaviour and outcome[11]. The DNA of pretherapeutic biopsies was genotyped for common genetic polymorphisms of MTHFR (5,10-methylenetetrahydrofolate reductase), MTR (Methionine synthase), and TS (thymidylate svnthase) tandem repeat polymorphisms. Tumors with an MTR wild-type genotype showed a shorter survival in contrast to tumors with an MTR variant genotype. This correlated with the response behaviour, where tumors with an MTR variant genotype responded more frequently to the neoadjuvant radiochemotherapy. In a subsequent study by Sarbia and colleagues, the expression of proteins involved in DNA repair and/or cell-cycle regulation, including p53 (phosphorylated at Ser15), EGFR (Epidermal Growth Factor Receptor), ATM (ataxia-telangiectasia mutated) protein kinase (phosphorylated at Ser1981), and checkpoint kinase 2 (CHK2) (phosphorylated at Thr68), was correlated with the response to RCTx and with overall survival[12]. Tumours that were positive for CHK2 expression more frequently showed clinically determined regression after RCTx than tumours that were negative for CHK2 expression, whereas other parameters did not correlate with tumour regression. Expression of ATM correlated with expression of CHK2 and p53-phospho. In contrast to histopathological response evaluation, none of the molecular parameters under investigation correlated with overall survival.

Other studies aimed to identify genes or proteins involved in resistance to 5-FU or cisplatin, found that 5-FU metabolism pathway genes, such as TS (thymidylate synthase), TP (thymidine phosphorylase), and DPD (dihydropyrimidine dehydrogenase), or genes involved in DNA-repair mechanisms, such as ERCC-1 (excision repair cross complementing), GSTP-1 (Glutathione S-transferase), or nm23-H1, were somewhat predictive for the response behaviour in patients with neoadjuvant radiochemotherapy. These studies were done either by immunohistochemistry or quantitative RT-PCR technologies[13,14].

Metallothionein (MT) is a small protein involved in many patho-physiological processes such as detoxification, cell proliferation, apoptosis, and therapy resistance. Kishi *et al*[15] demonstrated that high expression of this protein is associated with a poor prognosis due to non-response in patients with localized squamous cell cancer of the esophagus who received neoadjuvant radiochemotherapy. However, no such association could be found in another study by Harpole *et al*[16].

To date, however, none of these studies has shown one independent predictive factor on multivariate analysis.

With regard to molecular markers, the *p53* gene is one of the most widely investigated genes in human cancer. It has been found as a prognostic indicator in many different carcinomas[17,18]. It plays a crucial role in repairing DNA of damaged cells, is involved in triggering apoptosis, and might be intrinsically involved in the response to radiochemotherapy. Several studies have examined *p53* expression and the response to radiochemotherapy in esophageal cancer[19,20]. In patients with squamous cell cancer of the esophagus, Seitz *et al*[21] used immunohistochemistry to demonstrate a significant association of p53 overexpression and decreased response rates. Other groups have not found this association[22]. It is postulated that this difference might be due to gene deletion, failure of transcription, or a non-stabilizing mutation, all of which might lead to loss of p53 function[23].

The protein p21 is transcriptionally regulated by p53 by ionising radiation. This can cause cell cycle arrest and apoptosis. p21 is involved in disruption of regulatory networks and might be a good candidate gene for radioresistance prediction. However, as with many other single gene studies, the published results have been controversial. Some studies describe a positive correlation of p21 positivity and response or survival, while others were not able to demonstrate a correlation of p21 expression and response to radiochemotherapy[24-26].

Much research has been done in the past in studying COX-2 (Cyclooxygenase-2) expression and response in esophageal cancer. COX-2 plays an important role in

prostaglandin synthesis and is involved in angiogenesis and tumor growth. Results from cervical cancer demonstrating a predictive potential of COX-2 mRNA expression have been adapted to squamous cell cancer of the esophagus[27]. A study by Takatori *et al*[28] of 29 patients with esophageal squamous cell cancer who received neoadjuvant radiochemotherapy, found that high COX-2 mRNA expression in tumor biopsies was significantly associated with a poor response to radiochemotherapy and ultimately with a poor survival in these patients.

Another important aspect associated with molecular response prediction is growth regulation. Several proteins have been studied, such as epidermal growth factor receptor (EGFR), HER-2 (human epidermal growth factor receptor), and different cyclins. The results have been conflicting; for example HER-2 and cyclin D1 expressions have been found to be correlated with response to neoadjuvant radiochemotherapy in patients with squamous cell carcinoma of the esophagus, but failed to be predictive for the overall survival[29]. By studying EGFR and proliferating cell nuclear antigen, Hickey *et al*[30] reported an inverse relationship of response and expression in immunostaining of biopsies of patients with esophageal squamous cell cancer.

More convincing evidence was demonstrated by analysing VEGF (vascular endothelial growth factor) in the context of response prediction. VEGF is the major angiogenic factor in pathological angiogenesis. Angiogenesis plays a very important role in the promotion of tumor growth and formation of metastases. In a study by Shimada *et al*[31], co-expression of p53, TP, and VEGF (analysed by immunohistochemistry) was correlated to the response behaviour and survival in patients with squamous cell cancer of the esophagus. In a multivariate analysis, only VEGF emerged as a predictor of response to the neoadjuvant radiochemotherapy. Its expression was associated with a high incidence on non-responders and significantly worse survival. These results were supported by a study from Gorski and colleagues, who demonstrated that blocking the activity of VEGF enhances the effects of radiochemotherapy on the tumor[32]. The mechanisms behind this effect are not fully understood, but angiogenic factors seem to be a valuable clinical target for influencing the response behaviour in neoadjuvant treated squamous cell cancer of the esophagus.

One of the reasons for the conflicting results is the fact that most studies focused on single or few gene expression analyses. Tumor tissue has a very heterogeneous gene profile; therefore, the likelihood of finding a single gene responsible for the regulation of tumor resistance or sensitivity is very low. Recently, the introduction of RNA/DNA or protein microarrays opened the door for a variety of studies of molecular tumor profiling[33]. Duong *et al*[34] were able to demonstrate a positive predictive value of 100% and a negative predictive value of 79% in regards to response prediction in 21 patients with squamous cell carcinoma of the esophagus receiving neoadjuvant radiochemotherapy using SVM (support vector machine) modelling and LOOCV (Leave-one-out cross-validation) analyses as a multigene classifier. A 32-gene classifier was used to predict response to neoadjuvant radiochemotherapy. By further analyzing the specific genes involved in response prediction, most of the sequences were found to be involved in the apoptosis and angiogenesis pathways.

Serum markers

Several serum markers have been tested to predict response to neoadjuvant radiochemotherapy in patients with esophageal squamous cell cancer, including CEA (carcinoembryonic antigen), VEGF, and CYFRA (cytokeratin fragment) 21-1[35,36]. CYFRA was the only marker showing a close correlation between its serum level and response, but it has not been studied in a large prospective clinical trial.

Molecular imaging

The introduction of molecular imaging, such as FDG-PET (fluoro-deoxy-glucose-positron emission tomography) has changed the field with respect to the previous disappointing results of the conventional image methods in predicting response to neoadjuvant therapies. CT-scan, MRI, or EUS have failed to accurately predict tumor resistance or sensitivity. A recent meta-analysis found FDG-PET to be more accurate than a CT-scan for the measurement of treatment response[37]. There was no differentiation possible between inflammation, scars, and remnant carcinoma. FDG-PET is based on the high glucose metabolism of a tumor compared to normal tissue, enabling a good differentiation of tumor areas from non-tumor tissue. Recently, PET-CT-scans have combined the metabolism with anatomic location[38]. The relative changes in FDG uptake have been used for early response evaluation in a variety of tumor entities, such as breast[39], lung[40], and colon[41] cancer, as well as in Hodgkin's[42] and non Hodgkin's lymphoma[43]. There have been encouraging results in predicting response in patients with esophageal squamous cell cancer. Most studies performed the PET examination before the neoadjuvant radiochemotherapy and at the end of the preoperative protocol[44-48]. The relative decrease in standardized uptake value (SUV) between these two examinations served as a discriminator for response or non-response. The results were then correlated to the histopathological response assessment. By applying this approach, Brücher *et al*[48] were able to demonstrate a correlation between SUV decrease and histopathological response in 24 patients with esophageal squamous cell cancer. This was confirmed by other authors. Some even suggested that the absolute SUV of the initial PET might be sufficient to predict the response behaviour[45]. Recently, studies have been published with PET scans performed initially and two weeks into the neoadjuvant radiochemotherapy[45]. With the cut-off point at 30% reduction in SUV, a separation of responders from non-responders was possible after only two weeks with a sensitivity of 93% , a specificity of 88%, and an accuracy of 79%. Notably, non-responding patients who stopped the neoadjuvant chemotherapy after two weeks did not show a difference in survival compared to the patients who previously received the entire three months of chemo-

Table 2 Studies that have assessed the role of a PET scan in the response prediction of patients with neoadjuvant treated squamous cell cancer of the esophagus

Author	*n*	RCTx	2nd PET	Correlation of PET with histopathological response yes/no
Song *et al*[44], 2005	32	Cis/Cap/46 Gy	4 wk	Yes
Wieder *et al*[45], 2004	38	5 FU/40 Gy	During RCTx	Yes
Flamen *et al*[46], 2002	27	Cis/5-FU/40 Gy	After RCTx	Yes (tumor:liver ratio)
Kato *et al*[47], 2002	10	5-FU/30 Gy	After RCTx	No
Brücher *et al*[48], 2001	24	5-FU/30 Gy	After RCTx	Yes

PET: Positron emission tomography; Cis: Cisplatin; Cap: Capectabine; 5-FU: 5 Flurouracil; Gy: Gray; RCTx: Radiochemotherapy.

therapy. Without any decrease in survival, 2.5 months of chemotherapy could be avoided in these patients. At this time point, therapeutic regimens could be individual altered based on the PET results. Performing the 2nd PET-scan after one week of radiochemotherapy failed to predict the pathological response[49]. Table 2 shows a summary of the current available results of PET guided response evaluation on esophageal squamous cell cancer.

ADENOCARCINOMA OF THE ESOPHAGUS

Molecular response prediction

In patients with adenocarcinoma of the esophagus, the multimodal concepts differ considerably compared to the treatment regimens in squamous cell cancer. Some groups apply chemotherapy alone; others prefer a combination of radiation and chemotherapy in the multimodal setting. Therefore, it is difficult to compare the results of different studies. Additionally, adenocarcinoma of the esophagus is a much more heterogeneous tissue, with areas of invasive cancer, high-grade intraepithelial neoplasia, and the precursor lesion specialized intestinal metaplasia (Barrett's metaplasia) adjacent to each other. By taking single biopsies there is always a high risk of sampling error.

With regard to molecular response prediction, more work has been published for adenocarcinomas compared to squamous cell cancer of the esophagus. The introduction of quantitative high-throughput RT-PCR technologies, such as TaqMan, greatly increased the likelihood of identifying potential genes, or groups of genes, involved in response prediction. Most of the published studies focused on the analyses of drug targets involved in the metabolism of the most commonly used chemotherapy agents, such as 5-FU and platinum compounds. In a study by Langer *et al*[50] the quantitative RNA expression in biopsies of Barrett's carcinomas prior to the neoadjuvant chemotherapy of genes involved in the 5-FU metabolism (TS, TP, DPD, MTHFR, MAP7 (Mitogen-activated protein), and ELF3 (eukaryotic initiation factor) and platinum related genes, caldesmon, ERCC1, ERCC4, HER-2/neu, GADD45, and MRP1) were determined and compared to the histopathological response assessment of the postoperative specimen. There was a significant correlation between the pretherapeutic expression levels of MTHFR, caldesmon, and MRP1 with the histopathological response. Other groups found an association between TS, ERRC1, DPD, and GADD45 (growth arrest and DNA damage-inducible gene) and response[51,52].

In the past, p53 has been one of the most studied genes with regard to response prediction in esophageal adenocarcinoma, as well as in squamous cell cancer of the esophagus. Several trials found an inverse correlation between p53 positive tumors identified immunohistochemically and response. The entire apoptosis pathway seems to play a crucial role in the chemosensitivity of neoadjuvant treated Barrett carcinomas. Genes such as c-erbB-2, p53, p21, ki76, and bcl-2 (B-cell lymphoma) have been shown to be involved in response prediction[53]. These results were obtained either by immunohistochemistry or by quantitative RT-PCR methods.

The introduction of microarray technologies opened an entirely new area of response prediction on biopsy material. This has lead to a large increase in published studies that have enhanced our understanding of the biology of esophageal adenocarcinoma. Problems still arise from the difficulties in analysing the enormous amounts of data generated by these arrays. Different analytical approaches are currently available, such as unsupervised hierarchical cluster analysis of LOOCV analysis. The first published studies demonstrated promising results in identifying a cluster of 30-100 genes closely related to the response behaviour of these tumors. Furthermore, these gene expression studies identified some very interesting new genes that might serve as targets for new therapeutic approaches[54,55].

More recently, proteomic profiling has become feasible. First studies on cell lines assessing the chemosensitivity of a variety of cell lines, including esophageal cancer cell lines, provided the basis for the prediction of drug response based on protein markers[56]. A combination of these technologies might hold great promise for the future with regard to response prediction.

Currently, there is no reliable molecular marker for tumor response to neoadjuvant therapy. Early results are promising. Luthra *et al*[57] and Ashida *et al*[58] reported hierarchial clustering of gene expression profiles of esophageal carcinoma segregated samples into two major groups that correlated with response and identified genes differentially expressed between long- and short-term survival after neoadjuvant therapy for esophageal cancer. Additionally, Duong and colleagues[34] used a 32-gene classifier to predict response. These are all preliminary results, and to date, no clinical recommendations can be drawn from this.

Table 3 Studies that have assessed the role of a PET scan in the response prediction of patients with neoadjuvant treated Barrett's cancer and cancer of the gastroesophageal junction

Author	*n*	CTx	2nd PET	Correlation of PET with histopathological response yes/no
Lordick *et al*[60], 2007	110	Cis/5-FU	2 wk during CTx	Yes
Ott *et al*[59], 2006	65	Cis/5-FU	2 wk during CTx	Yes
Gillham *et al*[49], 2006	29	Cis/5-FU	After CTx	No
Levine *et al*[61], 2006	52	Cis/5-FU	After CTx	Yes
Swisher *et al*[62], 2004	73	Cis/5-FU/50,4 Gy Irin/5-FU/Taxol/50,4 Gy Taxol/Carbo/50,4 Gy	After RCTx	Yes
Brink *et al*[63], 2004	13	Cis/5-FU	After CTx	No
Arslan *et al*[64], 2002	22	Cis/Taxol/50,4 Gy	After RCTx	Yes
Weber *et al*[65], 2001	40	Cis/5-FU	2 wk during CTx	Yes

Cis: Cisplatin; Irin: Irinotecan; Carbo: Carboplatin; 5-FU: 5 Flurouracil; Gy: Gray; RCTx: Radiochemotherapy; CTx: Chemotherapy.

Molecular imaging

In Barrett's cancer, the use of PET-scan for the evaluation of response has been widely studied. These studies suggested that changes in FDG uptake in response to therapy correlates with the pathological response and predicts the risk of local recurrence and survival. Unfortunately, there have been no data published exclusively investigating the role of FDG-PET in adenocarcinoma of the esophagus. Therefore, it is difficult to assess the usefulness of PET imaging in predicting response to neoadjuvant chemotherapy in adenocarcinomas of the esophagus. The only good prospective trials were published in 2006 by Ott *et al*[59] followed by Lordick *et al*[60] in 2007. In the initial study on 65 patients with esophageal adenocarcinoma and some carcinoma at the cardia, the authors demonstrated that by taking a SUV decrease greater than 35% as the precondition of response, a prediction was possible during the neoadjuvant therapy after only two weeks. These results were correlated to the pathohistological response assessment on the operative specimen. This study was followed by a prospective trial where, for the first time, the therapy was tailored according to the changes in SUV uptake after two weeks. The responding group continued on chemotherapy followed by resection, whereas the group of patients who did not respond to the neoadjuvant chemotherapy discontinued chemotherapy after two weeks and proceeded directly to surgery. Complete histopathological response was noted in almost 60% of the PET responders in contrast to the PET non-responders, in which no histological response was noted. This first prospective trial confirmed the feasibility of a PET guided treatment plan after only two weeks of neoadjuvant chemotherapy. Other groups have also shown the value of PET scan in response prediction[61-65]. Based on these results, two major questions arose: (1) What treatment changes have to be made to the non-responders to increase the number of patients responding to the therapy? (2) Is it really necessary in the responder group to complete the entire cycle of neoadjuvant chemotherapy or is the biological selection after two weeks already sufficient for a prolongation in survival?

Table 3 lists the currently available data for PET guided response prediction in Barrett's cancer.

CONCLUSION

It is clear that the identification of predictors of response will change the management of patients with locally advanced adenocarcinoma and squamous cell cancer of the esophagus. Molecular imaging has conclusively shown that an early response evaluation is feasible after only two weeks of neoadjuvant therapy. The changes in SUV-uptake of PET scans prior to, and two weeks after, the beginning of the therapy correlated with the final histological response assessment and survival. Prospective trials have been published using this change in SUV uptake to tailor the therapy regimen accordingly.

It would be more desirable to predict the response prior to any kind of therapy. Several attempts have been made to predict response on the molecular level using biopsy material. Unfortunately, there are no single markers available at present that conclusively predict neoadjuvant therapy response. It is more likely that a panel of genes generated by microarray analyses or proteins detected by proteomics will be able to mirror the complex genetic behaviour of a tumor responding to chemotherapy or radiochemotherapy. Promising initial work is accumulating. Based on these data, a more individualized therapy of these patients could be performed with the ultimate goal of allowing as many patients as possible the survival benefit of a response to a neoadjuvant concept.

REFERENCES

1 **Altorki N**, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg* 2002; **236**: 177-183

2 **Lerut T**, Coosemans W, De Leyn P, Deneffe G, Topal B, Van de Ven C, Van Raemdonck D. Reflections on three field lymphadenectomy in carcinoma of the esophagus and gastroesophageal junction. *Hepatogastroenterology* 1999; **46**: 717-725

3 **Geh JI**, Crellin AM, Glynne-Jones R. Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer. *Br J Surg* 2001; **88**: 338-356

4 **Siewert JR**, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? *Semin Radiat Oncol* 2007; **17**: 38-44

5 **Suntharalingam M**, Moughan J, Coia LR, Krasna MJ, Kachnic L, Haller DG, Willett CG, John MJ, Minsky BD, Owen JB. The national practice for patients receiving radiation thera-

py for carcinoma of the esophagus: results of the 1996-1999 Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2003; **56**: 981-987
6 **Gebski V**, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; **8**: 226-234
7 **Adelstein DJ**, Rice TW, Becker M, Larto MA, Kirby TJ, Koka A, Tefft M, Zuccaro G. Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. *Cancer* 1997; **80**: 1011-1020
8 **Mandard AM**, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994; **73**: 2680-2686
9 **Becker K**, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Böttcher K, Siewert JR, Höfler H. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer* 2003; **98**: 1521-1530
10 **Chirieac LR**, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS, Roth JA, Rashid A, Hamilton SR, Wu TT. Post-therapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer* 2005; **103**: 1347-1355
11 **Sarbia M**, Stahl M, von Weyhern C, Weirich G, Pühringer-Oppermann F. The prognostic significance of genetic polymorphisms (Methylenetetrahydrofolate Reductase C677T, Methionine Synthase A2756G, Thymidilate Synthase tandem repeat polymorphism) in multimodally treated oesophageal squamous cell carcinoma. *Br J Cancer* 2006; **94**: 203-207
12 **Sarbia M**, Ott N, Pühringer-Oppermann F, Brücher BL. The predictive value of molecular markers (p53, EGFR, ATM, CHK2) in multimodally treated squamous cell carcinoma of the oesophagus. *Br J Cancer* 2007; **97**: 1404-1408
13 **Joshi MB**, Shirota Y, Danenberg KD, Conlon DH, Salonga DS, Herndon JE 2nd, Danenberg PV, Harpole DH Jr. High gene expression of TS1, GSTP1, and ERCC1 are risk factors for survival in patients treated with trimodality therapy for esophageal cancer. *Clin Cancer Res* 2005; **11**: 2215-2221
14 **Gillham CM**, Reynolds J, Hollywood D. Predicting the response of localised oesophageal cancer to neo-adjuvant chemoradiation. *World J Surg Oncol* 2007; **5**: 97
15 **Kishi K**, Doki Y, Miyata H, Yano M, Yasuda T, Monden M. Prediction of the response to chemoradiation and prognosis in oesophageal squamous cancer. *Br J Surg* 2002; **89**: 597-603
16 **Harpole DH Jr**, Moore MB, Herndon JE 2nd, Aloia T, D'Amico TA, Sporn T, Parr A, Linoila I, Allegra C. The prognostic value of molecular marker analysis in patients treated with trimodality therapy for esophageal cancer. *Clin Cancer Res* 2001; **7**: 562-569
17 **Quinlan DC**, Davidson AG, Summers CL, Warden HE, Doshi HM. Accumulation of p53 protein correlates with a poor prognosis in human lung cancer. *Cancer Res* 1992; **52**: 4828-4831
18 **Thomas DJ**, Robinson M, King P, Hasan T, Charlton R, Martin J, Carr TW, Neal DE. p53 expression and clinical outcome in prostate cancer. *Br J Urol* 1993; **72**: 778-781
19 **Ribeiro U Jr**, Finkelstein SD, Safatle-Ribeiro AV, Landreneau RJ, Clarke MR, Bakker A, Swalsky PA, Gooding WE, Posner MC. p53 sequence analysis predicts treatment response and outcome of patients with esophageal carcinoma. *Cancer* 1998; **83**: 7-18
20 **Lowe SW**, Ruley HE, Jacks T, Housman DE. p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. *Cell* 1993; **74**: 957-967
21 **Seitz JF**, Perrier H, Monges G, Giovannini M, Gouvernet J. [Multivariate analysis of the prognostic and predictive factors of response to concomitant radiochemotherapy in epidermoid cancers of the esophagus. Value of immunodetection of protein p53] *Gastroenterol Clin Biol* 1995; **19**: 465-474
22 **Lam KY**, Law S, Ma LT, Ong SK, Wong J. Pre-operative chemotherapy for squamous cell carcinoma of the oesophagus: do histological assessment and p53 overexpression predict chemo-responsiveness? *Eur J Cancer* 1997; **33**: 1221-1225
23 **Catalano V**, Baldelli AM, Giordani P, Cascinu S. Molecular markers predictive of response to chemotherapy in gastrointestinal tumors. *Crit Rev Oncol Hematol* 2001; **38**: 93-104
24 **Nakamura T**, Hayashi K, Ota M, Ide H, Takasaki K, Mitsuhashi M. Expression of p21(Waf1/Cip1) predicts response and survival of esophageal cancer patients treated by chemoradiotherapy. *Dis Esophagus* 2004; **17**: 315-321
25 **Nakashima S**, Natsugoe S, Matsumoto M, Kijima F, Takebayashi Y, Okumura H, Shimada M, Nakano S, Kusano C, Baba M, Takao S, Aikou T. Expression of p53 and p21 is useful for the prediction of preoperative chemotherapeutic effects in esophageal carcinoma. *Anticancer Res* 2000; **20**: 1933-1937
26 **Okumura H**, Natsugoe S, Matsumoto M, Mataki Y, Takatori H, Ishigami S, Takao S, Aikou T. The predictive value of p53, p53R2, and p21 for the effect of chemoradiation therapy on oesophageal squamous cell carcinoma. *Br J Cancer* 2005; **92**: 284-289
27 **Kim YB**, Kim GE, Pyo HR, Cho NH, Keum KC, Lee CG, Seong J, Suh CO, Park TK. Differential cyclooxygenase-2 expression in squamous cell carcinoma and adenocarcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2004; **60**: 822-829
28 **Takatori H**, Natsugoe S, Okumura H, Matsumoto M, Uchikado Y, Setoyama T, Sasaki K, Tamotsu K, Owaki T, Ishigami S, Aikou T. Cyclooxygenase-2 expression is related to prognosis in patients with esophageal squamous cell carcinoma. *Eur J Surg Oncol* 2008; **34**: 397-402
29 **Akamatsu M**, Matsumoto T, Oka K, Yamasaki S, Sonoue H, Kajiyama Y, Tsurumaru M, Sasai K. c-erbB-2 oncoprotein expression related to chemoradioresistance in esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **57**: 1323-1327
30 **Hickey K**, Grehan D, Reid IM, O'Briain S, Walsh TN, Hennessy TP. Expression of epidermal growth factor receptor and proliferating cell nuclear antigen predicts response of esophageal squamous cell carcinoma to chemoradiotherapy. *Cancer* 1994; **74**: 1693-1698
31 **Shimada H**, Hoshino T, Okazumi S, Matsubara H, Funami Y, Nabeya Y, Hayashi H, Takeda A, Shiratori T, Uno T, Ito H, Ochiai T. Expression of angiogenic factors predicts response to chemoradiotherapy and prognosis of oesophageal squamous cell carcinoma. *Br J Cancer* 2002; **86**: 552-557
32 **Gorski DH**, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, Seetharam S, Koons A, Hari DM, Kufe DW, Weichselbaum RR. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res* 1999; **59**: 3374-3378
33 **Schmidt U**, Begley CG. Cancer diagnosis and microarrays. *Int J Biochem Cell Biol* 2003; **35**: 119-124
34 **Duong C**, Greenawalt DM, Kowalczyk A, Ciavarella ML, Raskutti G, Murray WK, Phillips WA, Thomas RJ. Pretreatment gene expression profiles can be used to predict response to neoadjuvant chemoradiotherapy in esophageal cancer. *Ann Surg Oncol* 2007; **14**: 3602-3609
35 **Quillien V**, Raoul JL, Laurent JF, Meunier B, Le Prise E. Comparison of Cyfra 21-1, TPA and SCC tumor markers in esophageal squamous cell carcinoma. *Oncol Rep* 1998; **5**: 1561-1565
36 **Nakamura T**, Ide H, Eguchi R, Hayashi K, Takasaki K, Watanabe S. CYFRA 21-1 as a tumor marker for squamous cell carcinoma of the esophagus. *Dis Esophagus* 1998; **11**: 35-39
37 **Westerterp M**, van Westreenen HL, Reitsma JB, Hoekstra OS, Stoker J, Fockens P, Jager PL, Van Eck-Smit BL, Plukker JT, van Lanschot JJ, Sloof GW. Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy--systematic review. *Radiology* 2005; **236**: 841-851
38 **Bar-Shalom R**, Guralnik L, Tsalic M, Leiderman M, Frenkel A, Gaitini D, Ben-Nun A, Keidar Z, Israel O. The additional

value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2005; **32**: 918-924
39 **Schelling M**, Avril N, Nährig J, Kuhn W, Römer W, Sattler D, Werner M, Dose J, Jänicke F, Graeff H, Schwaiger M. Positron emission tomography using [(18)F]Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000; **18**: 1689-1695
40 **Thomas DM**, Mitchell PL, Berlangieri SU, Tochon-Danguy H, Knight S, Clarke CP, Scott AM. Positron emission tomography in assessing response to neoadjuvant chemotherapy for non-small-cell lung cancer. *Med J Aust* 1998; **169**: 227
41 **Yoshioka T**, Fukuda H, Fujiwara T, Iwata R, Ido T, Murakawa Y, Gamo M, Ishioka C, Kanamaru R. FDG PET evaluation of residual masses and regrowth of abdominal lymph node metastases from colon cancer compared with CT during chemotherapy. *Clin Nucl Med* 1999; **24**: 261-263
42 **Hueltenschmidt B**, Sautter-Bihl ML, Lang O, Maul FD, Fischer J, Mergenthaler HG, Bihl H. Whole body positron emission tomography in the treatment of Hodgkin disease. *Cancer* 2001; **91**: 302-310
43 **Okada J**, Yoshikawa K, Imazeki K, Minoshima S, Uno K, Itami J, Kuyama J, Maruno H, Arimizu N. The use of FDG-PET in the detection and management of malignant lymphoma: correlation of uptake with prognosis. *J Nucl Med* 1991; **32**: 686-691
44 **Song SY**, Kim JH, Ryu JS, Lee GH, Kim SB, Park SI, Song HY, Cho KJ, Ahn SD, Lee SW, Shin SS, Choi EK. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1053-1059
45 **Wieder HA**, Brücher BL, Zimmermann F, Becker K, Lordick F, Beer A, Schwaiger M, Fink U, Siewert JR, Stein HJ, Weber WA. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. *J Clin Oncol* 2004; **22**: 900-908
46 **Flamen P**, Van Cutsem E, Lerut A, Cambier JP, Haustermans K, Bormans G, De Leyn P, Van Raemdonck D, De Wever W, Ectors N, Maes A, Mortelmans L. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. *Ann Oncol* 2002; **13**: 361-368
47 **Kato H**, Kuwano H, Nakajima M, Miyazaki T, Yoshikawa M, Masuda N, Fukuchi M, Manda R, Tsukada K, Oriuchi N, Endo K. Usefulness of positron emission tomography for assessing the response of neoadjuvant chemoradiotherapy in patients with esophageal cancer. *Am J Surg* 2002; **184**: 279-283
48 **Brücher BL**, Weber W, Bauer M, Fink U, Avril N, Stein HJ, Werner M, Zimmerman F, Siewert JR, Schwaiger M. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. *Ann Surg* 2001; **233**: 300-309
49 **Gillham CM**, Lucey JA, Keogan M, Duffy GJ, Malik V, Raouf AA, O'byrne K, Hollywood D, Muldoon C, Reynolds JV. (18)FDG uptake during induction chemoradiation for oesophageal cancer fails to predict histomorphological tumour response. *Br J Cancer* 2006; **95**: 1174-1179
50 **Langer R**, Specht K, Becker K, Ewald P, Bekesch M, Sarbia M, Busch R, Feith M, Stein HJ, Siewert JR, Höfler H. Association of pretherapeutic expression of chemotherapy-related genes with response to neoadjuvant chemotherapy in Barrett carcinoma. *Clin Cancer Res* 2005; **11**: 7462-7469
51 **Theisen J**, Danenberg K, Ott K, Becker K, Danenberg P, Stein HJ, Siewert JR. Predictors of response and survival for neoadjuvant treated patients with esophageal adenocarcinoma. *Dis Esophagus* 2008; **21**: 601-606
52 **Warnecke-Eberz U**, Metzger R, Miyazono F, Baldus SE, Neiss S, Brabender J, Schaefer H, Doerfler W, Bollschweiler E, Dienes HP, Mueller RP, Danenberg PV, Hoelscher AH, Schneider PM. High specificity of quantitative excision repair cross-complementing 1 messenger RNA expression for prediction of minor histopathological response to neoadjuvant radiochemotherapy in esophageal cancer. *Clin Cancer Res* 2004; **10**: 3794-3799
53 **Duhaylongsod FG**, Gottfried MR, Iglehart JD, Vaughn AL, Wolfe WG. The significance of c-erb B-2 and p53 immunoreactivity in patients with adenocarcinoma of the esophagus. *Ann Surg* 1995; **221**: 677-683; discussion 683-684
54 **Luthra R**, Luthra MG, Izzo J, Wu TT, Lopez-Alvarez E, Malhotra U, Choi IS, Zhang L, Ajani JA. Biomarkers of response to preoperative chemoradiation in esophageal cancers. *Semin Oncol* 2006; **33**: S2-S5
55 **Schauer M**, Janssen KP, Rimkus C, Raggi M, Feith M, Friess H, Theisen J. Microarray based response prediction in esophageal adenocarcinomas. *Clin Can Res* 2009; In press
56 **Ma Y**, Ding Z, Qian Y, Shi X, Castranova V, Harner EJ, Guo L. Predicting cancer drug response by proteomic profiling. *Clin Cancer Res* 2006; **12**: 4583-4589
57 **Luthra R**, Wu TT, Luthra MG, Izzo J, Lopez-Alvarez E, Zhang L, Bailey J, Lee JH, Bresalier R, Rashid A, Swisher SG, Ajani JA. Gene expression profiling of localized esophageal carcinomas: association with pathologic response to preoperative chemoradiation. *J Clin Oncol* 2006; **24**: 259-267
58 **Ashida A**, Boku N, Aoyagi K, Sato H, Tsubosa Y, Minashi K, Muto M, Ohtsu A, Ochiai A, Yoshida T, Yoshida S, Sasaki H. Expression profiling of esophageal squamous cell carcinoma patients treated with definitive chemoradiotherapy: clinical implications. *Int J Oncol* 2006; **28**: 1345-1352
59 **Ott K**, Weber WA, Lordick F, Becker K, Busch R, Herrmann K, Wieder H, Fink U, Schwaiger M, Siewert JR. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol* 2006; **24**: 4692-4698
60 **Lordick F**, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007; **8**: 797-805
61 **Levine EA**, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, Melin SA, Lovato J, Oaks T, Blackstock AW. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. *Ann Surg* 2006; **243**: 472-478
62 **Swisher SG**, Erasmus J, Maish M, Correa AM, Macapinlac H, Ajani JA, Cox JD, Komaki RR, Hong D, Lee HK, Putnam JB Jr, Rice DC, Smythe WR, Thai L, Vaporciyan AA, Walsh GL, Wu TT, Roth JA. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. *Cancer* 2004; **101**: 1776-1785
63 **Brink I**, Hentschel M, Bley TA, Walch A, Mix M, Kleimaier M, Moser E, Imdahl A. Effects of neoadjuvant radio-chemotherapy on 18F-FDG-PET in esophageal carcinoma. *Eur J Surg Oncol* 2004; **30**: 544-550
64 **Arslan N**, Miller TR, Dehdashti F, Battafarano RJ, Siegel BA. Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. *Mol Imaging Biol* 2002; **4**: 301-310
65 **Weber WA**, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschläger G, Busch R, Siewert JR, Schwaiger M, Fink U. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol* 2001; **19**: 3058-3065

S- Editor Li LF **L- Editor** Stewart GJ **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.38

World J Gastrointest Surg 2009 November 30; 1(1): 38-48
ISSN 1948-9366 (online)

REVIEW

Malignant peritoneal mesothelioma

Stine Munkholm-Larsen, Christopher Q Cao, Tristan D Yan

Stine Munkholm-Larsen, Christopher Q Cao, Tristan D Yan, University of Sydney, Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney 2050, Australia
Stine Munkholm-Larsen, Christopher Q Cao, Tristan D Yan, Baird Institute for Applied Heart and Lung Surgical, Sydney 2050, Australia
Author contributions: Munkholm-Larsen S, Cao CQ and Yan TD designed and wrote the manuscript.
Correspondence to: Tristan D Yan, BSc (Med), MBBS, PhD, University of Sydney, Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney 2050, Australia. tristan.yan@unsw.edu.au
Telephone: +61-2-95155587 Fax: +61-2-95155587
Received: July 2, 2009 Revised: July 27, 2009
Accepted: August 4, 2009
Published online: November 30, 2009

Key words: Asbestos; Cisplatin; Cytoreductive surgery; Doxorubicin; Intraperitoneal chemotherapy; Mesothelin; Pemetrexed; Peritoneal mesothelioma; Peritonectomy

Peer reviewers: Dario Conte, Professor, GI Unit - IRCCS Osp. Maggiore, Chair of Gastroenterology, Via F. Sforza, 35, Milano 20122, Italy; Shingo Tsuji, MD, PhD, AGAF, Professor, Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine (A8), 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Munkholm-Larsen S, Cao CQ, Yan TD. Malignant peritoneal mesothelioma. *World J Gastrointest Surg* 2009; 1(1): 38-48 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/38.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.38

Abstract

Malignant mesothelioma is a highly aggressive neoplasm. The incidence of malignant mesothelioma is increasing worldwide. Diffuse malignant peritoneal mesothelioma (DMPM) represents one-fourth of all mesotheliomas. Association of asbestos exposure with DMPM has been observed, especially in males. The great majority of patients present with abdominal pain and distension, caused by accumulation of tumors and ascitic fluid. In the past, DMPM was considered a pre-terminal condition; therefore attracted little attention. Patients invariably died from their disease within a year. Recently, several prospective trials have demonstrated a median survival of 40 to 90 mo and 5-year survival of 30% to 60% after combined treatment using cytoreductive surgery and perioperative intraperitoneal chemotherapy. This remarkable improvement in survival has prompted new search into the medical science related to DMPM, a disease previously ignored as uninteresting. This review article focuses on the key advances in the epidemiology, diagnosis, staging, treatments and prognosis of DMPM that have occurred in the past decade.

INTRODUCTION

Malignant mesothelioma is a highly aggressive primary neoplasm of the serosal lining of the pleura, peritoneum, pericardium, or tunica vaginalis[1]. Probably because of extensive use of asbestos in building materials in the past, the incidence of malignant mesothelioma is increasing worldwide and is not expected to peak for another 5 to 20 years[2]. Diffuse malignant peritoneal mesothelioma (DMPM) is the second most common type of mesothelioma[1]. Patients who suffer from this disease usually present with abdominal pain or distension. As the disease progresses, they invariably die from intestinal obstruction or terminal starvation within a year. Due to the infrequent occurrence and the lack of understanding of the natural history of DMPM, traditionally there seemed to be a mutual agreement among medical practitioners that patients with this condition were preterminal. Few therapeutic advances have occurred in the last century since the disease was first described by Miller and Wynn in 1908[3]. Systemic chemotherapy, palliative surgery and/or total abdominal radiation therapy were used selectively, but did not seem to alter the natural history of this disease[4-10].

Recently, a reexamination of this disease including all aspects of diagnostic and treatment strategies has

emerged. This is related to the encouraging experiences in numerous centers with cytoreductive surgery and perioperative chemotherapy. This new treatment strategy has consistently demonstrated a markedly improved prognosis achieving a median survival of up to 90 mo and a 5-year survival of 60%[11-19]. The significant improvement achieved by this treatment modality offers a potentially curative option.

In addition, there has been substantial public interest in recent years, because millions of people have been exposed to asbestos in the environment, especially the workplace. The association with malignant mesothelioma, both pleural and peritoneal, has created considerable medical-legal implications involving billions of dollars in compensation costs for industry and government[20-22]. This review article focuses on the advances in the epidemiology, diagnosis, staging, management and prognosis of DMPM that have occurred in the past decade.

EPIDEMIOLOGY

The incidence of malignant mesothelioma has been rising worldwide since the 1970s, with some evidence recently of a slowing of this trend in some countries. In the United States, there was a steep rise in the incidence of mesothelioma through the 1990s, with a recent leveling off in the rate of increase, but no evidence that the peak incidence of mesothelioma has been passed in this country[21,23]. A similar pattern, with a plateauing of the incidence rate, is present in some European countries that reduced asbestos usage in a similar time frame to that in the United States[24-26]. However, the overall incidence of malignant mesothelioma is increasing worldwide and is not expected to peak for another 5 to 20 years[2]. A recent estimate for Great Britain is a peak incidence between 2011 and 2015[27] and the peak incidence in Norway is projected for 2010[28]. La Vecchia *et al*[29] used death certificates from 8 European countries to predict a peak mortality between 2010 and 2020; a peak incidence in France is expected in 2030[30] and is projected for 2012-2024 in Italy[31]. The incidence is expected to continue to increase in areas of the world where asbestos use has not been curtailed[32-34].

DMPM is the second most common type of malignant mesothelioma[1]. A recent analysis of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute estimated approximately 250 new cases of DMPM in the United States each year[21]. Some studies with an adequate number of cases demonstrated a strong association between the estimated occupational exposure to asbestos and the risk of DMPM, especially in males[20-22]. The overall incidence of this disease is higher in males than females, which may be related to a higher incidence of asbestos-related occupations in men[11]. DMPM has also been reported following radiation therapy, mica exposure, recurrent peritonitis and administration of thorium dioxide[35-39].

CLINICAL PRESENTATION

The initial symptoms and signs of DMPM are non-specific and due to the rarity of the disease, the level of clinical suspicion is relatively low[11,40]. Approximately 70% of patients have serous ascites, a product of the tumor nodules. This mixture of fluid and tumor buildup under pressure appears to be the major cause of morbidity. Increased abdominal girth (55%), pain (45%), and abdominal or pelvic mass (26%) are the most common initial complaints, which lead the physician to arrange for definitive tests resulting in a diagnosis of DMPM (Table 1)[11,40]. Unlike pleural mesothelioma, pain has not been found to have a significant negative impact on survival in patients with DMPM. Approximately 13% of patients present with new onset abdominal wall hernia, which is related to accumulated ascites and increased intraabdominal pressure. Other constitutional symptoms may also be present, such as weight loss (20%) and febrile episodes (10%), which were both associated with a reduced overall survival[11,40]. Tejido García *et al*[41] previously reported fever as an initial presentation of DMPM in 3 patients and hypothesized that fever constitutes the initial clinical presentation only when the disease remains asymptomatic until it is far advanced. In females, approximately 25% seek medical attention as a result of non-specific gynecological symptoms, such as pelvic mass or infertility[11]. Lymphadenopathy or distant organ metastasis is extremely rare in this disease. Five percent of patients may present with concomitant pleural effusion.

Table 1 Symptoms and signs of DMPM

Symptoms
Abdominal pain (40%)
Abdominal distension (40%)
Constitutional symptoms, such as weight loss and fever (20%)
Incidental finding (10%)
Signs
Ascites (70%)
Abdominal or pelvic mass (30%)
Abdominal wall hernia (10%)
Guarding and rebound tenderness (10%)
Pleural effusion (5%)

DMPM: Diffuse malignant peritoneal mesothelioma.

DIAGNOSIS

Macroscopically, DMPM is characterized by thousands of whitish tumor nodules of variable size and consistency. These nodules may coalesce to form plaques or masses or layer out evenly to cover part, or the entirety of the peritoneal surface (Figure 1).

Radiology

Evolutionary change has occurred in the technology of computed tomography (CT). With administration of adequate intravenous, oral and rectal contrast media, multislice CT is the current mainstay imaging tool for patients with DMPM. It allows more precise identification and evaluation of DMPM than sonography. In the past, several studies described the radiologic appearances of DMPM in small case-series of fewer than 10 patients[42-44].

Yan *et al*[45] studied preoperative abdominal and pelvic

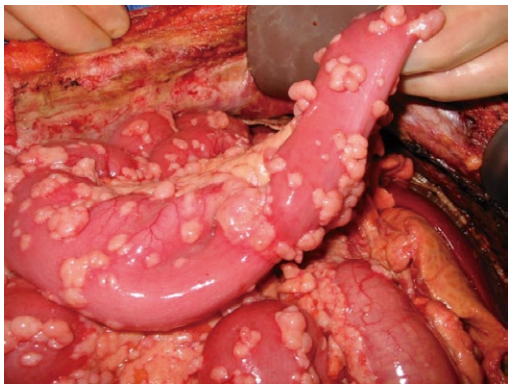


Figure 1 Macroscopically, diffuse malignant peritoneal mesothelioma (DMPM) is characterized by thousands of whitish tumor nodules of variable size and consistency that may coalesce to form plaques or masses or layer out evenly to cover the entire peritoneal surface.

Table 2 CT characterization of DMPM

CT characterization of DMPM
Diffuse involvement of all peritoneal surface, rarely with an epicenter
Preponderance of disease in mid-abdomen and pelvic
Presence of serous ascites rather than mucoid
Absence of metastasis, irrespective of the volume of disease

CT: Computed tomography.

CT scans of 33 DMPM patients in a systematic manner and identified four radiologic characteristics that could be used to distinguish DMPM from other peritoneal carcinomatosis (Table 2). First, the authors studied the distribution of DMPM and determined that this disease was diffuse throughout the peritoneal cavity. The lack of a primary site for this disease distinguished it from peritoneal dissemination from gastrointestinal or gynecologic malignancies. Second, the most heavily disease-involved regions were the mid-abdomen and pelvis. In contrast to pseudomyxoma peritonei or other diseases causing mucinous carcinomatosis, compartmentalization of the small bowel and a large volume of disease beneath the right hemidiaphragm were absent. Third, the presence of serous ascites rather than mucinous ascites was commonly seen in DMPM. Fourth, none of the patients had extra abdominal lymph node or distant organ metastasis. One must raise the clinical suspicion of DMPM in patients with serous ascites, no primary tumors and yet a disease process that remains confined to the abdominopelvic cavity.

Magnetic resonance imaging (MRI) provides good contrast resolution, but requires longer scan times during which respiratory motion and bowel peristalsis can interfere with the image resolution. Positron emission tomography (PET) may be useful and provide functional imaging, but the ability to detect diffuse small tumor nodules is limited. However, PET-CT may be able to provide high CT resolution with simultaneous PET functional imaging. The efficacy of these radiologic modalities in the assessment of DMPM remains to be evaluated.

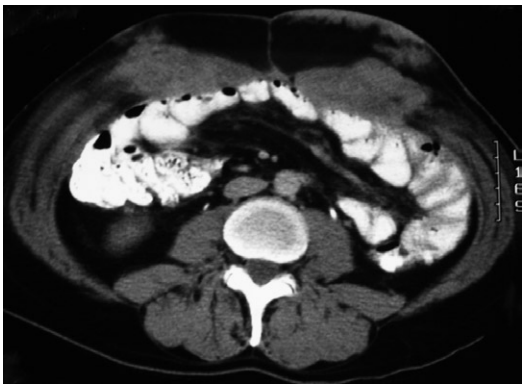


Figure 2 DMPM implantation in the lateral abdominal wall along previous laparoscopic trochar tracts.

Biopsy

Commonly, a long delay in the definitive diagnosis of DMPM is a significant problem for both the physician and the patient. Cytological examination of ascitic fluid removed by paracentesis rarely results in a positive finding[46]. If cells are recovered, they frequently resemble hyperplasic mesothelial cells with insufficient atypia present for a confident diagnosis. The state-of-the-art approach to histological verification of the diagnosis of peritoneal malignancy is a CT-guided biopsy, or a laparoscopy. In a study population of 68 DMPM patients, Sugarbaker *et al*[11] found very few definitive diagnoses made by paracentesis and cytology. Laparoscopy with biopsy was required in 52%, laparotomy with biopsy in 44% and a radiologic guided biopsy in 4%[11]. Eltabbakh and colleagues performed laparotomy or laparoscopy with biopsy as the definitive test for all 15 DMPM patients[10]. Four of the 15 patients had preoperative paracentesis, but all were reported as adenocarcinoma. The low reliability of cytological results warrants an invasive procedure to obtain a generous sample of peritoneal tumor in patients with peritoneal surface cancer of uncertain etiology.

However, an important caveat must accompany the recommendation for laparoscopy in the diagnosis of DMPM. In a series of 8 patients with DMPM diagnosed by laparoscopy, 6 patients presented with tumor implantation in the lateral abdominal wall around trochar tracts (Figure 2), resulting in extraperitoneal dissemination, which changed the natural history of the disease[47]. Therefore, lateral port sites for laparoscopy must be avoided. Trochars should only be placed within the linea alba, so that port sites can be excised at the time of definitive surgical treatment.

Immunohistochemical stains

A biopsy of the tumor is subjected to a complete histopathological analysis. However, the distinction of DMPM from adenocarcinoma is subtle both macroscopically and on routine microscopic study. A series of immunohistochemical markers are necessary to differentiate DMPM from adenocarcinoma (Table 3)[1]. Calretinin identifies cells as being mesothelial in origin. A positive

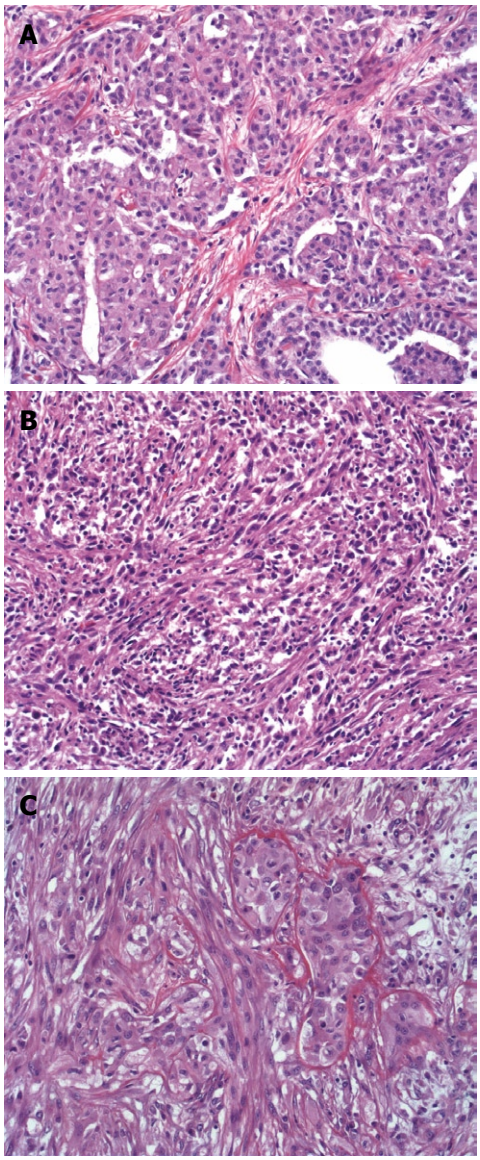


Figure 3 Histopathology of DMPM. A: DMPM-epithelial type, characterized by cuboidal or flattened epithelial-like malignant mesothelial cells (HE, × 20); B: Sarcomatoid type, characterized by sarcomatous spindle-shaped mesothelial cells (HE, × 20); C: Biphasic type, characterized by presence of two phenotypes occurred in same tumor, but sometimes they are intimately admixed (HE, × 20).

calretinin, cytokeratins 5/6, WT-1, thrombomodulin, and mesothelin stain, accompanied by a negative B72.3, CEA, CD 15, Leu-M1, and BER-EP4 immunostain is highly suggestive of DMPM.

Histopathology

DMPM has a diversity of cytoarchitectural characteristics that are almost unique among neoplasms originating from a single cell line. The spectrum embraces tumors that are entirely of epithelial or mesenchymal (sarcomatoid) type to a range of biphasic and intermediate forms, as described by Battifora and McCaughey[1].

75% to 90% of DMPM are of the epithelial type, which are characterized by cuboidal or flattened epithelial-like malignant mesothelial cells with ample cytoplasm with distinct cellular membranes, and a relatively uniform, granular to vesicular nuclei (Figure 3A). The subtypes of epithelial DMPM are categorized by the patterns observed for the malignant epithelial component, which are classified as tubulopapillary, solid, deciduoid, storiform-like, fascicular-like, multicystic, papillary, microcystic and granular.

The sarcomatoid DMPM is composed only of spindle-shaped mesenchymal type cells (Figure 3B). However, the mesenchymal portion can be as diverse as the epithelial component, in that the sarcomatous elements may morphologically and immunophenotypically resemble any one of the numerous bone and soft tissue tumors by producing malignant osteoid, cartilage or other sarcomatous histologies.

In biphasic DMPM, malignant elements of both epithelial and mesenchymal appearance are present (Figure 3C). Frequently, the two phenotypes occurred in different parts of the same tumor, but sometimes they are intimately admixed. There is sometimes a high degree of subjectivity involved in the diagnosis of pure sarcomatoid *versus* biphasic DMPM, which depends on the amount of tissue available and the extent to which it is sampled.

Table 3 Immunostains of diffuse malignant peritoneal mesothelioma and adenocarcinoma

Immunostains	Mesothelioma	Adenocarcinoma
BER-EP4	0-11	90-100
B27.3	0-5	81
Calretinin	42-100	6-9
CA-125	14-94	90
CD15 (LEU-MI)	0-10	58-100
CEA	0-10	90-100
EMA	80-100	83
P53	45	43-53
PAN-Cytokeratin	100	100
PLAP	0	50
VIMENTIN	40	0-6
S-100	0-11	31

Serum markers

Serum CA-125, a tumor antigen that is present in the majority of patients with ovarian cancer, is also elevated in DMPM. In a study by Kebapci *et al*[48], CA-125 levels were measured at diagnosis in eight patients with DMPM. Seven patients (6 females and 1 male) had CA-125 values > 32.0 U/mL (normal value 1.2-32 U/mL). In three of these patients serum CA-125 returned to normal levels after chemotherapy. A study by Simsek *et al*[49] also noted elevated CA-125 in 6 of 7 DMPM patients and in some patients showed a very close correlation with the response to chemotherapy.

Recently, several new tumor markers have been identified to diagnosis mesothelioma. These studies have mostly involved patients with pleural mesothelioma. However, given the similarity between pleural and peritoneal mesothelioma, it is likely that these tests will also be useful in peritoneal mesothelioma. These new tumor markers include mesothelin, soluble mesothelin related proteins (SMRP) and osteopontin. Mesothelin is a cell surface pro-

tein highly expressed in mesotheliomas that is attached to the cell surface by a glycosylphosphatidyl inositol (GPI) linkage[50]. Since many GPI-linked proteins are shed into the serum by proteolytic cleavage of the GPI anchor, Hassan and colleagues developed an enzyme-linked immunosorbent assay (ELISA) to determine if mesothelin is shed into the blood. Using this assay an increased serum mesothelin level in 71% of mesothelioma patients was identified[51]. The investigators also looked at serum mesothelin levels before and at several time points after tumor debulking surgery in 6 patients with DMPM; they showed that serum mesothelin levels decreased very rapidly after optimal tumor debulking and may therefore be a useful marker to monitor response to therapy. Another assay that measures SMRP noted elevated levels of SMRP in 37 of 44 patients (84%) with pleural mesothelioma and these levels correlated with tumor bulk[52]. Osteopontin, a glycoprotein that is overexpressed in several cancers, was recently found to be elevated in the serum of patients with pleural mesothelioma. More importantly, serum osteopontin levels were increased in patients with early pleural mesothelioma (stage I) and could therefore be a useful test for early detection[53]. It is very likely that these newly described biomarkers will also be of use for the diagnosis and monitoring of treatment response in patients with DMPM.

MANAGEMENT

Systemic chemotherapy

Traditionally, there has been an agreement among medical practitioners that DMPM was untreatable and thus a preterminal condition with a rapid progression. Patients were managed with systemic chemotherapy and palliative surgery. However, all patients eventually died from the disease as a result of intestinal obstruction and/or terminal starvation[4-10]. The median survival in these patients prior to the year 2000 was less than one year (Table 4) [4-10]. There are now Food and Drug Administration-approved treatment protocols using systemic pemetrexed plus cisplatin. A recent non-randomized study demonstrated a median survival of 13 mo and 1-year survival of 66% in 66 DMPM patients treated with systemic pemetrexed and cisplatin, *versus* 9 mo and 0% in the respective survival for 32 DMPM patients treated with systemic pemetrexed alone[54]. From the limited data, it is difficult to extrapolate any definitive conclusions regarding the efficacy of this systemic chemotherapy treatment, but further research is warranted.

Intraperitoneal chemotherapy

Several studies have evaluated chemotherapy administered *via* the intraperitoneal route in an attempt to maximize local-regional cytotoxicity and limit systemic side-effects[7,55,56]. However, intraperitoneal chemotherapy penetrates tumor nodules by passive diffusion; therefore the depth of penetration is limited. In addition, the efficacy of intraperitoneal chemotherapy is reduced due to limited chemotherapy distribution in a grossly diseased abdomen. No studies have demonstrated survival benefit for intraperitoneal chemotherapy alone for DMPM.

Table 4 Median survival of DMPM using traditional treatment modalities

Authors	*n*	Median survival (mo)
Chailleux *et al*[4], 1988	11/167	10[1]
Antman *et al*[5], 1988	37/180	15[1]
Sridhar *et al*[6], 1992	13/50	9.5[1]
Markman *et al*[7], 1992	19	9
Yates *et al*[8], 1997	14/272	14[1]
Neumann *et al*[9], 1999	74	12
Eltabbakh *et al*[10], 1999	15	12.5

[1]Combined pleural and peritoneal mesothelioma.

Cytoreductive surgery and perioperative intraperitoneal chemotherapy

Recently, there has been a reexamination of DMPM treatment, by cytoreductive surgery and perioperative intraperitoneal chemotherapy with intent not to palliate, but to cure[11-19]. There have already been several large studies, including a randomized controlled trial examining the efficacy of this combined procedure for the management of peritoneal carcinomatosis from gastrointestinal and ovarian malignancies[57-62]. DMPM remains confined within the peritoneal cavity throughout its clinical course and these patients experience morbidity and mortality almost exclusively as a result of disease progression in the abdominopelvic cavity. The combined locoregional treatment approach has a strong treatment rationale for DMPM patients.

Cytoreductive surgery is an important first step in the combined treatment; it maximally removes peritoneal tumors together with complete lysis of adhesions between the bowel loops. It consists of a series of peritonectomy procedures including: anterior parietal peritonectomy, greater omentectomy with splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy with cholecystectomy, and pelvic peritonectomy with rectosigmoid colonic resection[63]. This provides an optimal situation for adjuvant intraperitoneal chemotherapy, which is given before the formation of any adhesions, allowing direct chemotherapy and tumor-cell contact, without necessarily increasing systemic toxicity[64,65]. Hyperthermia has been known to have direct cytotoxic effects in both a temperature and time-dependent manner[66,67]. It has also been shown to allow a greater depth of penetration of the chemotherapy agents into the tumors and synergize the cytotoxic drugs selected for intraperitoneal use at the time of surgery[68-70].

The most recent phase Ⅱ study from the National Cancer Institute, Bethesda, USA showed that the median survival of 49 DMPM patients was 92 mo, with a 5-year survival rate of 59%, after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy[14]. The National Cancer Institute of Italy also enrolled 49 patients to undergo the combined treatment and reported that the progression-free survival was 40 mo and the 5-year survival was 57%[16]. Washington Cancer Institute, Washington DC, USA recently published an updated series on 100 DMPM patients who underwent the combined treatment, which

Table 5 Recent updates on cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for DMPM

Authors	*n*	Median survival (mo)	Survival rates (%)				
			1-yr	2-yr	3-yr	5-yr	7-yr
Yan *et al*[19], 2006	100	52	78	64	55	46	39
Feldman *et al*[14], 2003	49	92	86	77	59	59	-
Deraco *et al*[16], 2006	49	NR	88	74	65	57	-
Brigand *et al*[17], 2006	15	36	69	58	43	29	-
Loggie *et al*[18], 2001	12	34	60	60	50	33	33

NR: Median survival was not reached.

demonstrated that overall median survival was 52 mo, with 5- and 7-year survival of 46% and 39%, respectively[19]. Table 5 demonstrates the most recently published updates from all international treatment centers[14,16-19].

Despite the favorable survival data of the combined treatment for DMPM as compared to traditional palliative therapies in the current literature, the results should be interpreted with caution for several reasons. Firstly, the survival benefit is achieved at the expense of moderate to high morbidity and mortality rates, especially at treatment centers in the process of overcoming their initial learning curve. The results achieved by international experts in this field may not be replicated in routine clinical practice. The importance of patient selection is highlighted in the following sections. Second, being a tertiary referral center with multiple patient selection factors operating, the sample studied may not be a valid representation of the targeted population. Thirdly, results of the combined treatment *versus* traditional therapies should be interpreted with the knowledge that these treatment strategies have not been compared directly. A phase Ⅲ trial would be ideal. However, this will be difficult to achieve in the current setting, as a comparison between a potentially curative treatment option with a palliative procedure may cause patients to decline randomization. Also, it may be impractical due to the rarity of the disease, as a sufficient number of patients are required. However, a well-designed prospective multi-institutional study may be potentially meaningful.

Radiotherapy

The efficacy of radiotherapy alone for patients with DMPM is unclear. It has been used as an adjunct to other multi-modality treatments in an attempt to achieve aggressive disease control. Taub *et al*[71] performed a prospective single-institution phase Ⅰ/Ⅱ trial on 27 patients with DMPM. The treatment regimen consisted of initial exploratory laparotomy with cytoreductive surgery and placement of indwelling intraperitoneal catheters. Four intraperitoneal courses of doxorubicin (25 mg) alternating with four intraperitoneal courses of cisplatin (100 mg/m^2) were administered. Four intraperitoneal doses of gamma interferon were given followed by a second laparotomy with biopsy verification of complete response or attempted resection of residual disease. Intraperitoneal hyperthermic chemotherapy with mitomycin (10 mg/m^2) plus cisplatin (75 to 100 mg/m^2), followed by whole abdominal radiation was added to the management plan. The overall median survival was 68 mo with a 3-year survival of 67%[71].

Immunotherapy

There is limited data regarding the role of immunotherapy in peritoneal mesothelioma because of a lack of clinical trials specifically targeting this patient population. However, some information is available from Phase I studies that have included DMPM patients. In a phase I study of Flt3 immunotherapy, 15 patients were treated with intraperitoneal or subcutaneous Flt3-L[72]. The treatment was well tolerated. Of the four DMPM patients treated in this study, two had stable disease lasting 8 mo. Another study evaluated intraperitoneal administration of human interleukin-12[73]. Although this trial included only one DMPM patient, the patient had a complete response for 2 years. Investigators at the National Cancer Institute, Bethesda are conducting clinical studies targeting the tumor antigen, mesothelin. Mesothelin is a cell surface protein present on normal mesothelial cells lining the pleura, peritoneum and pericardium that is highly expressed in mesothelioma, ovarian and pancreatic cancer[50]. To target mesothelin they have developed a recombinant immunotoxin, SS1P, consisting of an anti-mesothelin Fv linked to a truncated Pseudomonas exotoxin. In a Phase I study of SS1P, 23 patients with mesothelin-expressing cancers including 8 patients with DMPM were treated[74]. In this study, one patient with DMPM had complete resolution of abdominal ascites lasting more than 3 years and has required no further treatment. Given the rarity of DMPM, efficacy studies of promising immunotherapy agents will require well-designed multi-institutional clinical trials.

PROGNOSTIC FACTORS AND STAGING

In the past, no uniform treatments were suggested for patients with DMPM and the survival was largely dependent upon the indolent *versus* aggressive biology of the disease. Several studies reported a reduced survival outcome associated with biphasic or sarcomatoid histologic type, as compared to epithelial type[11,14,75]. However, the criterion is not useful as a prognostic indicator, because the majority of DMPM patients are diagnosed with the epithelial type. There was in fact no staging system for DMPM. A lack of prognostic indicators for optimal patient selection is not surprising. As the disease is rare, most centers do not have a sufficient number of patients. Treatments employed in these patients have varied greatly. Most studies in the current literature have a relatively small sample size and the clinical implications of these reports, in terms of their value for patient management, are limited.

In the last 5 years, several international treatment centers have demonstrated a markedly improved survival in DMPM patients after the combined treatment, compared to historical controls[11-19]. As increased numbers of patients are treated with a uniform regimen, a more thorough and precise analysis of clinical, radiologic and histopathologic prognostic parameters are possible.

Gender

Females have been found to show a better prognosis in DMPM, as compared to males[11]. A very real epidemiologic difference between males and females appears to be the likelihood of asbestos exposure. The direct exposure to asbestos was definitely causative in men, but less apparent in women[20,22]. It is possible that this difference in causation is at least in part responsible for the difference in the natural history of DMPM in women. However, other clinical characteristics may contribute to the improved prognosis of females. In the authors' previous study, women seldom presented with weight loss; a lack of this important poor prognostic symptom suggests less advanced disease[40]. Also, women often sought medical attention earlier with gynecological complaints caused by DMPM. Diagnosis as a result of non-specific gynecological symptoms may have contributed to their improved long-term survival[11]. A recent study showed that females were associated with more favorable histopathologic features, which also might contribute to their better overall outcome[76].

Lymph node metastasis

Lymph node metastasis is uncommon in patients with DMPM, but is associated with an extremely poor prognosis[19]. In 100 DMPM patients treated at the Washington Cancer Institute, seven patients were found to have positive lymph nodes. The most common sites of lymph node involvement were external, internal and common iliac lymph nodes, and ileocolic lymph nodes. Their median survival was 6 mo, with 1- and 2-year survival of 43% and 0%, respectively. Ninety-three patients had absence of lymph node involvement and their median survival was 59 mo, with 5- and 7-year survival of 50% and 43%, respectively[19]. Apparently, lymph node metastasis in DMPM uniformly indicates a guarded prognosis. The crucial importance of lymph node positivity *versus* negativity in DMPM encourages the surgeon to be diligent in seeking abnormal lymph nodes when performing cytoreductive surgery. Any enlarged or firm lymph nodes should be submitted separately from the rest of the specimens. It should become current surgical practice to sample some iliac lymph nodes and all suspicious lymph nodes in patients with DMPM in order to definitively establish their lymph node status.

Completeness of cytoreduction

Nearly all treatment centers agree that completeness of cytoreduction is one of the most significant prognostic factors for long-term survival[11-19]. It is related to the pretreatment tumor load and the surgeon's ability to eradicate gross disease. Unlike pseudomyxoma peritonei or other mucinous adenocarcinoma, DMPM does not spare the peritoneal surfaces of the small intestines. This unfortunately limits the ability to achieve a complete cytoreduction. However, even an adequate cytoreduction with a residual tumor < 2.5 cm in diameter, combined with perioperative intraperitoneal chemotherapy can offer some patients long-term benefits. International experience has consistently shown that after an adequate cytoreduction and perioperative intraperitoneal chemotherapy, the 5-year survival ranges from 30% to 60%[11-19].

Table 6 Interpretative CT classification of small bowel and small bowel mesentery for DMPM

Class	Interpretative CT classification of small bowel and small bowel mesentery
0	No ascites in the region of the small bowel; no evidence of peritoneal tumor present; the jejunal and ileal vessels appear as round and curvilinear densities within the mesenteric fat
I	Free ascites only; mesentery is stranded and stratified as the fluid accumulation outlined the small bowel mesentery; small bowel vessels are easily identified within the mesenteric fat
II	Tumor involvement of small bowel and/or its mesentery; peritoneal surface is thickened and enhanced due to the presence of tumor nodules or plaques; there may be an increased amount of ascites and the mesentery may appear stellate or pleated
III	Increased solid tumor involvement and adjacent small bowel loops are matted together in some cuts; small bowel mesenteric vessels are difficult to define due to obliteration of mesenteric fat

Radiologic classifications

There are problems with using completeness of cytoreduction for prognostication, as this clinical information is unavailable preoperatively in the patient selection process. Yan *et al*[77] described interpretive CT classifications of the small bowel and mesentery, which are useful in determining the operability of a patient with DMPM. As indicated in Table 6, characteristic interpretative CT appearances of the small bowel and its mesentery are categorized into four classes (Class 0-Ⅲ). In Class Ⅲ disease, configuration of the small bowel and mesentery on CT appears so thickened and grossly distorted that an adequate cytoreduction is almost impossible to achieve[77].

Histopathologic staging

In 1995, Goldblum and Hart first described a nuclear grading system according to histomorphologic features of DMPM[78]. In 2001, Kerrigan and colleagues first tested this nuclear grading system in 25 female patients with DMPM who underwent a variety of surgical, chemotherapy or radiotherapy treatments and found that the nuclear grading was not strongly associated with long-term survival[79]. In 2005, Nonaka and co-workers demonstrated that the size of the mesothelioma nucleus was prognostically significant for overall survival in 35 patients who underwent uniform treatment using cytoreductive surgery and perioperative intraperitoneal chemotherapy[15].

In 2006, with a larger sample size, uniform treatment, longer follow-up and more histopathology sections per patients studied, Yan and collaborators found in multivariate analysis that the nuclear size was the only independent prognostic determinant for overall survival in DMPM[12]. The 3-year survival rates with nuclear size of 10-20 μm, 21-30 μm, 31-40 μm and > 40 μm were 100%, 87%, 27% and 0%, respectively (Figure 4)[12]. The findings may suggest that nuclear size is a surrogate molecular marker of the biological aggressiveness of DMPM. The prognosis of patients with DMPM after

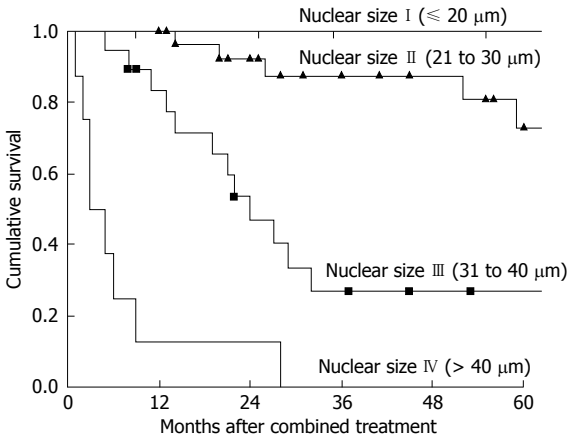


Figure 4 Cumulative survival after cytoreductive surgery and perioperative intraperitoneal chemotherapy for DMPM. The prognostic significance of mesothelioma nuclear size was $P < 0.001$.

maximal attempt of cytoreduction and perioperative intraperitoneal chemotherapy is predominantly governed by the biological aggressiveness of the mesothelioma cells. It seems that this combined treatment offers little survival benefit to patients with a nucleus size of > 40 μm. Consequently, the authors have proposed a histopathologic staging system using nuclear size only, as an objective and quantitative assessment of the predominant nuclear size of DMPM[12].

Future directions

Asbestos is predicted to cost the economy of the western world around $US 300 billion in compensation in future decades. This is in addition to health-care costs associated with the disease. Many unanswered questions remain regarding the management of DMPM. For example, is there now a role for long-term bi-directional (intravenous and intraperitoneal) chemotherapy as reported in ovarian cancer[62]. This disease, which has always been considered a pre-terminal condition, can now be treated with curative-intent by cytoreductive surgery and perioperative intraperitoneal chemotherapy at a referral center with benefit in terms of long-term survival. This new treatment approach may also result in quality of life benefit in that there is a complete resolution of ascites in most patients. Perhaps it is safe to suggest that this new combined treatment option is a new standard of care with which all other treatment options should now be compared. With more patients undergoing a uniform treatment plan, a deeper understanding can be gained in the diagnosis, radiology and histopathology of this rare disease.

Despite numerous studies demonstrating promising survival advantages and acceptable perioperative outcomes associated with the combined treatment, as shown in the present review, there is a lack of high-level evidence or comparative data on the safety and effectiveness of the combined treatment *versus* current alternative therapies. Recruitment of adequate numbers of patients for a randomized controlled trial to evaluate the comparative safety and effectiveness of these procedures for DMPM is difficult, as the period of time required to recruit an adequate number of patients to reach any statistical difference is likely to extend over different evolutions of both the intervention and comparator. In addition, there might be unwillingness from both patients and healthcare providers to randomize patients to receive a potentially curative treatment against a palliative approach.

Under these circumstances, high quality prospective observational data collection will be extremely important, as it provides more accurate estimates of safety and efficacy outcomes for the procedure, in addition to evaluating potential prognostic factors associated with favourable outcomes. More importantly, outcomes must be recorded on an intention-to-treat basis. Many centers report outcomes only in patients who are accepted for aggressive management strategies and who received complete cytoreduction. Although this may be predictive of outcome, it only applies to selected patients, usually with favourable prognostic features. This is not useful in terms of patient selection. Ideally, establishment of a multi-institutional registry requiring a minimum data set for all patients and recording treatment outcomes regardless of the intervention they received would provide more reliable estimates of outcomes for patients receiving different therapies over a longer term.

We propose a multi-institutional registry database that would collect the following information: (1) data on all DMPM patients in whom complete cytoreduction and perioperative intraperitoneal chemotherapy is attempted, regardless of whether or not peritonectomy is performed, whether or not optimal cytoreduction is achieved or an open-and-close laparotomy is performed; (2) clinicopathologic information including demographic data, radiological findings, lymph node status, systemic metastases, extent of intraperitoneal disease and histopathological grading; (3) surgical intervention details including components of cytoreductive surgery, types of visceral resections, application of perioperative intraperitoneal chemotherapy, completeness of cytoreduction, operation time and transfusion requirement; (4) short-term outcomes including in-hospital mortality, moderate to severe morbidity, including Grade Ⅲ/Ⅳ chemotherapy-related toxicity, intra-abdominal abscess, fistula, anastomotic leak, sepsis, pulmonary embolism, radiological interventions, complications requiring return to operating room and intensive care unit; (5) delayed complications including post-discharge morbidity and readmissions and (6) regular patient follow-up performed at set intervals for effectiveness including 5-year overall survival, minimum 2-year disease-free/progression-free survival, quality of life after acute treatment effects.

It is possible that this approach to observational data collection may also provide some information on prognostically similar patients undergoing different management pathways, thereby providing some evidence for a comparison of different treatment options. In addition, the roles of systemic chemotherapy, immunotherapy and targeted treatments in DMPM patients remain to be studied and their integration into the combined therapy has yet to be determined.

REFERENCES

1 **Battifora H**, McCaughey WTE. Tumors of the Serosal Membranes. Washington DC: Armed Forces Institute of Pathology, 1994
2 **Robinson BW**, Lake RA. Advances in malignant mesothelioma. *N Engl J Med* 2005; **353**: 1591-1603
3 **Miller J**, Wynn H. A malignant tumour arising from the endothelium of the peritoneum, and producing a mucoid ascitic fluid. *J Pathol Bacteriol* 2005; **12**: 267-268
4 **Chailleux E**, Dabouis G, Pioche D, de Lajartre M, de Lajartre AY, Rembeaux A, Germaud P. Prognostic factors in diffuse malignant pleural mesothelioma. A study of 167 patients. *Chest* 1988; **93**: 159-162
5 **Antman K**, Shemin R, Ryan L, Klegar K, Osteen R, Herman T, Lederman G, Corson J. Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965-1985. *J Clin Oncol* 1988; **6**: 147-153
6 **Sridhar KS**, Doria R, Raub WA Jr, Thurer RJ, Saldana M. New strategies are needed in diffuse malignant mesothelioma. *Cancer* 1992; **70**: 2969-2979
7 **Markman M**, Kelsen D. Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma. *J Cancer Res Clin Oncol* 1992; **118**: 547-550
8 **Yates DH**, Corrin B, Stidolph PN, Browne K. Malignant mesothelioma in south east England: clinicopathological experience of 272 cases. *Thorax* 1997; **52**: 507-512
9 **Neumann V**, Müller KM, Fischer M. [Peritoneal mesothelioma--incidence and etiology] *Pathologe* 1999; **20**: 169-176
10 **Eltabbakh GH**, Piver MS, Hempling RE, Recio FO, Intengen ME. Clinical picture, response to therapy, and survival of women with diffuse malignant peritoneal mesothelioma. *J Surg Oncol* 1999; **70**: 6-12
11 **Sugarbaker PH**, Welch LS, Mohamed F, Glehen O. A review of peritoneal mesothelioma at the Washington Cancer Institute. *Surg Oncol Clin N Am* 2003; **12**: 605-621, xi
12 **Yan TD**, Brun EA, Cerruto CA, Haveric N, Chang D, Sugarbaker PH. Prognostic indicators for patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma. *Ann Surg Oncol* 2007; **14**: 41-49
13 **Park BJ**, Alexander HR, Libutti SK, Wu P, Royalty D, Kranda KC, Bartlett DL. Treatment of primary peritoneal mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP). *Ann Surg Oncol* 1999; **6**: 582-590
14 **Feldman AL**, Libutti SK, Pingpank JF, Bartlett DL, Beresnev TH, Mavroukakis SM, Steinberg SM, Liewehr DJ, Kleiner DE, Alexander HR. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. *J Clin Oncol* 2003; **21**: 4560-4567
15 **Nonaka D**, Kusamura S, Baratti D, Casali P, Cabras AD, Younan R, Rosai J, Deraco M. Diffuse malignant mesothelioma of the peritoneum: a clinicopathological study of 35 patients treated locoregionally at a single institution. *Cancer* 2005; **104**: 2181-2188
16 **Deraco M**, Nonaka D, Baratti D, Casali P, Rosai J, Younan R, Salvatore A, Cabras Ad AD, Kusamura S. Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. *Ann Surg Oncol* 2006; **13**: 229-237
17 **Brigand C**, Monneuse O, Mohamed F, Sayag-Beaujard AC, Isaac S, Gilly FN, Glehen O. Peritoneal mesothelioma treated by cytoreductive surgery and intraperitoneal hyperthermic chemotherapy: results of a prospective study. *Ann Surg Oncol* 2006; **13**: 405-412
18 **Loggie BW**, Fleming RA, McQuellon RP, Russell GB, Geisinger KR, Levine EA. Prospective trial for the treatment of malignant peritoneal mesothelioma. *Am Surg* 2001; **67**: 999-1003
19 **Yan TD**, Yoo D, Sugarbaker PH. Significance of lymph node metastasis in patients with diffuse malignant peritoneal mesothelioma. *Eur J Surg Oncol* 2006; **32**: 948-953
20 **Welch LS**, Acherman YI, Haile E, Sokas RK, Sugarbaker PH. Asbestos and peritoneal mesothelioma among college-educated men. *Int J Occup Environ Health* 2005; **11**: 254-258
21 **Price B**, Ware A. Mesothelioma trends in the United States: an update based on Surveillance, Epidemiology, and End Results Program data for 1973 through 2003. *Am J Epidemiol* 2004; **159**: 107-112
22 **Spirtas R**, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, Harlow BL, Benichou J. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 1994; **51**: 804-811
23 **Weill H**, Hughes JM, Churg AM. Changing trends in US mesothelioma incidence. *Occup Environ Med* 2004; **61**: 438-441
24 **Montanaro F**, Bray F, Gennaro V, Merler E, Tyczynski JE, Parkin DM, Strnad M, Jechov'a M, Storm HH, Aareleid T, Hakulinen T, Velten M, Lef'evre H, Danzon A, Buemi A, Daur'es JP, Ménégoz F, Raverdy N, Sauvage M, Ziegler H, Comber H, Paci E, Vercelli M, De Lisi V, Tumino R, Zanetti R, Berrino F, Stanta G, Langmark F, Rachtan J, Mezyk R, Blaszczyk J, Ivan P, Primic-Zakelj M, Martínez AC, Izarzugaza I, Borràs J, Garcia CM, Garau I, Sánchez NC, Aicua A, Barlow L, Torhorst J, Bouchardy C, Levi F, Fisch T, Probst N, Visser O, Quinn M, Gavin A, Brewster D, Mikov M. Pleural mesothelioma incidence in Europe: evidence of some deceleration in the increasing trends. *Cancer Causes Control* 2003; **14**: 791-803
25 **Langård S**. Nordic experience: expected decline in the incidence of mesotheliomas resulting from ceased exposure? *Med Lav* 2005; **96**: 304-311
26 **Swuste P**, Burdorf A, Ruers B. Asbestos, asbestos-related diseases, and compensation claims in The Netherlands. *Int J Occup Environ Health* 2004; **10**: 159-165
27 **McElvenny DM**, Darnton AJ, Price MJ, Hodgson JT. Mesothelioma mortality in Great Britain from 1968 to 2001. *Occup Med* (Lond) 2005; **55**: 79-87
28 **Ulvestad B**, Kjaerheim K, Møller B, Andersen A. Incidence trends of mesothelioma in Norway, 1965-1999. *Int J Cancer* 2003; **107**: 94-98
29 **La Vecchia C**, Decarli A, Peto J, Levi F, Tomei F, Negri E. An age, period and cohort analysis of pleural cancer mortality in Europe. *Eur J Cancer Prev* 2000; **9**: 179-184
30 **Banaei A**, Auvert B, Goldberg M, Gueguen A, Luce D, Goldberg S. Future trends in mortality of French men from mesothelioma. *Occup Environ Med* 2000; **57**: 488-494
31 **Marinaccio A**, Montanaro F, Mastrantonio M, Uccelli R, Altavista P, Nesti M, Costantini AS, Gorini G. Predictions of mortality from pleural mesothelioma in Italy: a model based on asbestos consumption figures supports results from age-period-cohort models. *Int J Cancer* 2005; **115**: 142-147
32 **Dave SK**, Beckett WS. Occupational asbestos exposure and predictable asbestos-related diseases in India. *Am J Ind Med* 2005; **48**: 137-143
33 **Kazan-Allen L**. Asbestos and mesothelioma: worldwide trends. *Lung Cancer* 2005; **49** Suppl 1: S3-S8
34 **Chang KC**, Leung CC, Tam CM, Yu WC, Hui DS, Lam WK. Malignant mesothelioma in Hong Kong. *Respir Med* 2006;

100: 75-82
35 **Antman KH**, Corson JM, Li FP, Greenberger J, Sytkowski A, Henson DE, Weinstein L. Malignant mesothelioma following radiation exposure. *J Clin Oncol* 1983; **1**: 695-700
36 **Chahinian AP**, Pajak TF, Holland JF, Norton L, Ambinder RM, Mandel EM. Diffuse malignant mesothelioma. Prospective evaluation of 69 patients. *Ann Intern Med* 1982; **96**: 746-755
37 **Riddell RH**, Goodman MJ, Moossa AR. Peritoneal malignant mesothelioma in a patient with recurrent peritonitis. *Cancer* 1981; **48**: 134-139
38 **Maurer R**, Egloff B. Malignant peritoneal mesothelioma after cholangiography with thorotrast. *Cancer* 1975; **36**: 1381-1385
39 **Peterson JT Jr**, Greenberg SD, Buffler PA. Non-asbestos-related malignant mesothelioma. A review. *Cancer* 1984; **54**: 951-960
40 **Acherman YI**, Welch LS, Bromley CM, Sugarbaker PH. Clinical presentation of peritoneal mesothelioma. *Tumori* 2003; **89**: 269-273
41 **Tejido García R**, Anta Fernández M, Hernández Hernández JL, Bravo González J, González Macías J. [Fever of unknown origin as the clinical presentation of malignant peritoneal mesothelioma] *An Med Interna* 1997; **14**: 573-575
42 **Reuter K**, Raptopoulos V, Reale F, Krolikowski FJ, D'Orsi CJ, Graham S, Smith EH. Diagnosis of peritoneal mesothelioma: computed tomography, sonography, and fine-needle aspiration biopsy. *AJR Am J Roentgenol* 1983; **140**: 1189-1194
43 **Ros PR**, Yuschok TJ, Buck JL, Shekitka KM, Kaude JV. Peritoneal mesothelioma. Radiologic appearances correlated with histology. *Acta Radiol* 1991; **32**: 355-358
44 **Guest PJ**, Reznek RH, Selleslag D, Geraghty R, Slevin M. Peritoneal mesothelioma: the role of computed tomography in diagnosis and follow up. *Clin Radiol* 1992; **45**: 79-84
45 **Yan TD**, Haveric N, Carmignani CP, Bromley CM, Sugarbaker PH. Computed tomographic characterization of malignant peritoneal mesothelioma. *Tumori* 2005; **91**: 394-400
46 **Yu GH**, Soma L, Hahn S, Friedberg JS. Changing clinical course of patients with malignant mesothelioma: implications for FNA cytology and utility of immunocyto-chemical staining. *Diagn Cytopathol* 2001; **24**: 322-327
47 **Muensterer OJ**, Averbach AM, Jacquet P, Otero SE, Sugarbaker PH. Malignant peritoneal mesothelioma. Case-report demonstrating pitfalls of diagnostic laparoscopy. *Int Surg* 1997; **82**: 240-243
48 **Kebapci M**, Vardareli E, Adapinar B, Acikalin M. CT findings and serum ca 125 levels in malignant peritoneal mesothelioma: report of 11 new cases and review of the literature. *Eur Radiol* 2003; **13**: 2620-2626
49 **Simsek H**, Kadayifci A, Okan E. Importance of serum CA 125 levels in malignant peritoneal mesothelioma. *Tumour Biol* 1996; **17**: 1-4
50 **Hassan R**, Bera T, Pastan I. Mesothelin: a new target for immunotherapy. *Clin Cancer Res* 2004; **10**: 3937-3942
51 **Hassan R**, Remaley AT, Sampson ML, Zhang J, Cox DD, Pingpank J, Alexander R, Willingham M, Pastan I, Onda M. Detection and quantitation of serum mesothelin, a tumor marker for patients with mesothelioma and ovarian cancer. *Clin Cancer Res* 2006; **12**: 447-453
52 **Robinson BW**, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N, Winzell P, Hellstrom KE, Hellstrom I. Mesothelin-family proteins and diagnosis of mesothelioma. *Lancet* 2003; **362**: 1612-1616
53 **Pass HI**, Lott D, Lonardo F, Harbut M, Liu Z, Tang N, Carbone M, Webb C, Wali A. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. *N Engl J Med* 2005; **353**: 1564-1573
54 **Jänne PA**, Wozniak AJ, Belani CP, Keohan ML, Ross HJ, Polikoff JA, Mintzer DM, Taylor L, Ashland J, Ye Z, Monberg MJ, Obasaju CK. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer* 2005; **7**: 40-46
55 **Markman M**. Intraperitoneal belly bath chemotherapy. 2nd ed. Chicago: Percept Press, 1990
56 **Vlasveld LT**, Gallee MP, Rodenhuis S, Taal BG. Intraperitoneal chemotherapy for malignant peritoneal mesothelioma. *Eur J Cancer* 1991; **27**: 732-734
57 **Verwaal VJ**, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; **21**: 3737-3743
58 **Verwaal VJ**, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; **12**: 65-71
59 **Glehen O**, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, Barone R, Yonemura Y, Cavaliere F, Quenet F, Gutman M, Tentes AA, Lorimier G, Bernard JL, Bereder JM, Porcheron J, Gomez-Portilla A, Shen P, Deraco M, Rat P. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; **22**: 3284-3292
60 **Glehen O**, Mithieux F, Osinsky D, Beaujard AC, Freyer G, Guertsch P, Francois Y, Peyrat P, Panteix G, Vignal J, Gilly FN. Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. *J Clin Oncol* 2003; **21**: 799-806
61 **Sugarbaker PH**. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 2006; **7**: 69-76
62 **Armstrong DK**, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006; **354**: 34-43
63 **Sugarbaker PH**. Peritonectomy procedures. *Ann Surg* 1995; **221**: 29-42
64 **Katz MH**, Barone RM. The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. *Surg Oncol Clin N Am* 2003; **12**: 673-688
65 **Sugarbaker P**, Cunliffe W, Belliveau J, Bruin E, Graves T. Rationale for perioperative intraperitoneal chemotherapy as a surgical adjunct for gastrointestinal malignancy. *Reg Cancer Treat* 1988; 66-79
66 **Armour EP**, McEachern D, Wang Z, Corry PM, Martinez A. Sensitivity of human cells to mild hyperthermia. *Cancer Res* 1993; **53**: 2740-2744
67 **Los G**, Smals OA, van Vugt MJ, van der Vlist M, den Engelse L, McVie JG, Pinedo HM. A rationale for carboplatin treatment and abdominal hyperthermia in cancers restricted to the peritoneal cavity. *Cancer Res* 1992; **52**: 1252-1258
68 **Los G**, Sminia P, Wondergem J, Mutsaers PH, Havemen J, ten Bokkel Huinink D, Smals O, Gonzalez-Gonzalez D, McVie JG. Optimisation of intraperitoneal cisplatin therapy with regional hyperthermia in rats. *Eur J Cancer* 1991; **27**: 472-477
69 **van de Vaart PJ**, van der Vange N, Zoetmulder FA, van

Goethem AR, van Tellingen O, ten Bokkel Huinink WW, Beijnen JH, Bartelink H, Begg AC. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. *Eur J Cancer* 1998; **34**: 148-154

70 **Urano M**, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. *Int J Hyperthermia* 1999; **15**: 79-107

71 **Taub RN**, Hesdorffer ME, Keohan ML. Combined resection, intraperitoneal chemotherapy, and whole abdominal radiation for malignant periotneal mesothelioma (MPM). *J Clin Oncol* 2005; **23**: 664s

72 **Freedman RS**, Vadhan-Raj S, Butts C, Savary C, Melichar B, Verschraegen C, Kavanagh JJ, Hicks ME, Levy LB, Folloder JK, Garcia ME. Pilot study of Flt3 ligand comparing intraperitoneal with subcutaneous routes on hematologic and immunologic responses in patients with peritoneal carcinomatosis and mesotheliomas. *Clin Cancer Res* 2003; **9**: 5228-5237

73 **Lenzi R**, Rosenblum M, Verschraegen C, Kudelka AP, Kavanagh JJ, Hicks ME, Lang EA, Nash MA, Levy LB, Garcia ME, Platsoucas CD, Abbruzzese JL, Freedman RS. Phase I study of intraperitoneal recombinant human interleukin 12 in patients with Müllerian carcinoma, gastrointestinal primary malignancies, and mesothelioma. *Clin Cancer Res* 2002; **8**: 3686-3695

74 **Hassan R**, Bullock S, Kindler H, Pastan I. Updated results of the phase I study of SS1(dsFv)PE38 for targeted therapy of mesothelin expressing cancers. *Eur J Cancer* 2004; **2**: 280A

75 **Sebbag G**, Yan H, Shmookler BM, Chang D, Sugarbaker PH. Results of treatment of 33 patients with peritoneal mesothelioma. *Br J Surg* 2000; **87**: 1587-1593

76 **Yan TD**, Popa E, Brun EA, Cerruto CA, Sugarbaker PH. Sex difference in diffuse malignant peritoneal mesothelioma. *Br J Surg* 2006; **93**: 1536-1542

77 **Yan TD**, Haveric N, Carmignani CP, Chang D, Sugarbaker PH. Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Cancer* 2005; **103**: 839-849

78 **Goldblum J**, Hart WR. Localized and diffuse mesotheliomas of the genital tract and peritoneum in women. A clinicopathologic study of nineteen true mesothelial neoplasms, other than adenomatoid tumors, multicystic mesotheliomas, and localized fibrous tumors. *Am J Surg Pathol* 1995; **19**: 1124-1137

79 **Kerrigan SA**, Turnnir RT, Clement PB, Young RH, Churg A. Diffuse malignant epithelial mesotheliomas of the peritoneum in women: a clinicopathologic study of 25 patients. *Cancer* 2002; **94**: 378-385

S- Editor Li LF **L- Editor** Webster JR **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.49

World J Gastrointest Surg 2009 November 30; 1(1): 49-55
ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Gastric cancer surgery for patients with liver cirrhosis

Yoshiyuki Ikeda, Tatsuo Kanda, Shin-ichi Kosugi, Kazuhito Yajima, Atsushi Matsuki, Tsutomu Suzuki, Katsuyoshi Hatakeyama

Yoshiyuki Ikeda, Tatsuo Kanda, Shin-ichi Kosugi, Kazuhito Yajima, Atsushi Matsuki, Katsuyoshi Hatakeyama, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata 951-8510, Japan

Tsutomu Suzuki, Department of Nursing, School of Health Sciences, Niigata University, 2-746 Asahimachi-dori, Niigata, 951-8518, Japan

Author contributions: Ikeda Y and Kanda T conducted and wrote the majority of this study; Kosugi S, Yajima K, Matsuki A, Suzuki T and Hatakeyama K were involved in editing the manuscript.

Correspondence to: Tatsuo Kanda, MD, PhD, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Niigata 951-8510, Japan. kandat@med.niigata-u.ac.jp
Telephone: +81-25-2272228 Fax: +81-25-2270779

Received: October 20, 2009 Revised: November 12, 2009
Accepted: November 19, 2009
Published online: November 30, 2009

Abstract

AIM: To elucidate the influence of liver cirrhosis (LC) on the prognosis of patients with gastric cancer (GC).

METHODS: Of the 1347 GC patients who underwent curative gastrectomy for GC between January 1984 and June 2007, 25 patients (21 men and 4 women with a median age of 67 years; range 54-77 years) with LC were enrolled in this study. Using the Child-Pugh classification, 15 patients were evaluated as grade A and 10 patients as grade B. No grade C patient underwent gastrectomy in this series. Clinical outcomes, including postoperative morbidity and survival, were retrospectively analyzed based on medical records and surgical files.

RESULTS: There was no significant difference in operative blood loss and perioperative blood transfusion between the two groups. The most common postoperative complication was intractable ascites, which was the single postoperative morbidity noted more frequently in grade B patients (40.0%) than in grade A patients (6.7%) with statistical significance (P = 0.041). Operative mortality due to hepatic failure was seen in one grade A patient. Three patients had hepatocellular carcinoma (HCC) at presentation and two patients developed HCC after surgery. Overall 5-year survival rate was 58.9% in patients with early GC and 33.3% in patients with advanced GC (P = 0.230). GC-specific 5-year survival rate of early GC patients was 90.0% while that of advanced GC patients was 58.3% (P = 0.010). Four patients with early GC died of uncontrolled HCC, of which two were synchronous and two metachronous.

CONCLUSION: The risk of postoperative intractable ascites is high, particularly in grade B patients. Early detection and complete control of HCC is vital to improve a patient's prognosis.

Key words: Gastric cancer; Liver dysfunction; Surgery

Peer reviewer: Yun-Fei Yuan, Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng Road E., Guangzhou 510060, Guangdong Province, China

Ikeda Y, Kanda T, Kosugi S, Yajima K, Matsuki A, Suzuki T, Hatakeyama K. Gastric cancer surgery for patients with liver cirrhosis. *World J Gastrointest Surg* 2009; 1(1): 49-55 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/49.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.49

INTRODUCTION

Two clinical problems should be considered in the management of gastric cancer (GC) patients with liver cirrhosis (LC): safety of the surgery and patient prognosis, which is potentially worsened by a LC-related death in the long term.

It is well known that patients with LC have a high

incidence of postoperative complications and postoperative mortality[1-4]. Several studies assessing the risk of GC surgery in LC-complicated patients have been reported and the usefulness of the Child classification has been noted[5,6]. However, although the Child classification is convenient and widely used, its lack of objectivity is a cause for concern. Recently, the Child-Pugh classification[7], which replaces assessment factors with laboratory data and scores them, is more frequently used to evaluate overall hepatic function. However, it remains uncertain whether or not this modified classification is sufficiently reliable to assess the risk of GC surgery as only a limited number of studies have been conducted.

With regard to the prognosis of patients with GC associated with LC, Isozaki *et al*[6] reported that the 5-year survival rate after gastrectomy is 64% in patients with early GC and 14% in those with advanced GC. In a recent multicenter, retrospective study on patients with GC associated with LC conducted in South Korea[8], the 5-year survival rate was 73% in patients with early GC and 26% in those with advanced GC. These studies have shown that the prognosis is poorer in patients with GC associated with LC than in GC patients with no complications. Early studies have shown that LC-related deaths, including hepatic failure, esophagogastric bleeding and liver cancer, may have lowered overall patient survival. However, data on the incidence, treatment and outcome of LC-related diseases or the impact on patient survival are lacking. Clearly, the prognosis of GC patients with LC is affected not only by GC but also by LC and synchronous or metachronous hepatocellular carcinoma (HCC). Therefore, to determine the therapeutic strategy for GC associated with LC, it is necessary to know precisely the effects of LC-related diseases on the prognosis of patients after GC surgery.

In this study, the usefulness of risk assessment of GC surgery based on the currently used Child-Pugh classification was evaluated. In addition, by investigating in detail the prognosis of patients, the effects of LC and LC-related diseases on the long-term prognosis of patients with GC are shown.

MATERIALS AND METHODS

Patients

A total of 1347 consecutive patients underwent a gastrectomy for GC at Niigata University Medical and Dental Hospital between January 1984 and June 2007. Of the 1347 GC patients, 25 (1.9%) were diagnosed as having LC and these 25 patients were enrolled in this study. The diagnosis of LC was made on the basis of clinical findings and laboratory tests. Clinical findings included preoperative imaging and intraoperative findings. The presence or absence of ascites, splenomegaly, irregularity of liver surface, atrophy of the right lobe, and hypertrophy of the left lobe were evaluated by abdominal ultrasonography and computed tomography. Diffuse scarring of the liver, characterized by loss of lobular architecture and the formation of regenerative nodules, was a typical finding. Intraoperative liver biopsy performed in 4 of the 25 patients confirmed the histological diagnosis of LC based on the presence of fibrous septa and regenerative nodules. The patients were comprised of 21 men (84.0%) and 4 women (16.0%) with a median age of 67 years (range 54-77 years). Of the 25 GC patients with LC in this study, 15 patients were evaluated as grade A and 10 as grade B using the Child-Pugh classification. There were no grade C patients who underwent a gastrectomy in this series. The median follow-up time was 45 mo (range 6-168 mo).

Preoperative assessment of liver damage

To assess the severity of liver damage, the Child-Pugh classification was used. Laboratory tests included serologic tests for hepatitis B virus surface antigen (HBV) and hepatitis C virus antibody (HCV), hematochemical tests, and coagulation tests for grading using the Child-Pugh classification. Indocyanine green (ICG) disappearance rate was determined and used as an indicator of hepatic functional reserve in 20 patients. After intravenous injection of ICG (0.5 mg/kg), plasma ICG disappearance rate (K-ICG) was calculated by linear regression from plasma ICG concentrations at 5, 10 and 15 min.

Tumor, surgery, postoperative morbidity, and mortality

The description of GC, including primary lesions, metastatic lesions, staging, surgical treatment and histological findings, was recorded in accordance with the Japanese Classification of Gastric Carcinoma[9]. Early cancer was defined as a T1 tumor while advanced cancer was defined as ⩾ a T2 tumor, regardless of nodal involvement.

A total or distal gastrectomy was selected depending on the location and the macroscopic type of GC. When the tumor was located in the middle or lower third of the stomach, a distal gastrectomy was performed. When the cancer-free margin could not be ensured by a distal gastrectomy due to an infiltrative growth pattern, a total gastrectomy was selected regardless of the main location of the tumor. A modified gastrectomy A was defined as a gastrectomy with lymph node dissection of all Group 1 nodes in addition to lymph nodes along the left gastric artery according to GC treatment guidelines[10]. A wedge resection was performed when a patient had early GC and limited hepatic functional reserve (ICG retention rate at 15 min > 40%), or when it was necessary to perform a portosystemic shunt operation simultaneously due to serious esophageal varices.

Postoperative morbidity included intractable ascites (abdominocentesis and/or increased diuretics required), hepatic failure [clinical manifestations of edema, ascites, hyperbilirubinemia (defined as serum total bilirubin > 2.0 mg/dL), and ammonemia (defined as blood ammonia > 100 μg/dL)], intraabdominal infection (positive bacterial culture of drainage fluid), anastomotic leakage, and sepsis (proven by blood culture). Postoperative mortality was defined as any death occurring during the hospital stay for the gastrectomy.

Statistical analysis

Pearson's χ^2 test and Fisher's exact test were used to analyze

associations for the comparison of two factors. Overall survival was calculated from the time of gastrectomy until death from any cause or the most recent follow-up for surviving patients. GC-specific survival rate was calculated from the time of gastrectomy until death from GC. Survival curves were estimated using the Kaplan-Meier method and compared by means of the log-rank test. The Mann-Whitney test was used to compare continuous variables between groups. All statistical evaluations were performed using StatView version 5.0 software (SAS Institute, Cary, NC, USA). All tests were two-sided and values of $P < 0.05$ were considered statistically significant.

RESULTS

Clinical characteristics and gastric cancer treatment

The results of preoperative blood studies, laboratory tests, and coagulation tests of the 25 patients are shown in Table 1. Significant decreases in hemoglobin, platelet count, serum albumin, and prothrombin time were found in the grade B group as compared to the grade A group. Total bilirubin, aspartate aminotransferase and hepatic functional reserve determined using ICG, were not significantly different between the two groups.

The clinicopathological characteristics of the 25 patients using the Child-Pugh classification are shown in Table 2. The most common cause of cirrhosis was alcohol in the grade A group and virus in the grade B group. The grade B group had significantly more patients with intraoperative ascites than the grade A group ($P = 0.001$). Distal gastrectomy, total gastrectomy, and wedge resection were performed in 12 (48.0%), 10 (40.0%), and 3 (12.0%) patients, respectively. Three patients underwent a total gastrectomy with splenectomy and a further 3 patients underwent a splenectomy and caudal pancreatectomy for complete lymph node dissection. A D1 dissection was the most common extent of lymph node dissection, most of which were conducted in combination with a modified gastrectomy A. None of the patients presented with a residual tumor macroscopically after gastrectomy. Sixteen tumors (64.0%) were histologically diagnosed as early cancer, while 9 (36.0%) were diagnosed as advanced cancer. Lymph node metastasis was microscopically found in 5 patients (20.0%). Depth of invasion, lymph node metastasis, extent of gastric resection, and that of lymph node dissection were not significantly different between the two groups.

Intra- and postoperative surgical outcomes

Table 3 compares operative blood loss, perioperative blood transfusion of packed red blood cells (PRBC) and fresh frozen plasma (FFP), and postoperative morbidity and mortality between the two groups. Operative blood loss and perioperative blood transfusion were not significantly different between the two groups although the mean amounts were larger in the grade B group. The most common postoperative complication was intractable ascites which was the only postoperative morbidity noted more frequently in grade B patients (40.0%) than in grade A patients (6.7%) with statistical significance. Postoperative hospital stay was not significantly different between the two groups.

Table 1 Preoperative assessment using the Child-Pugh classification

	Grade A (n = 15)	Grade B (n = 10)	P value
Hemoglobin (g/dL)	13.5 ± 2.0	10.2 ± 2.8	0.006
Platelet (104/μL)	13.0 ± 6.1	9.3 ± 9.6	0.040
Albumin (g/dL)	3.9 ± 0.5	3.0 ± 0.4	0.001
Total bilirubin (mg/dL)	0.8 ± 0.3	0.9 ± 0.5	0.696
Aspartate aminotransferase (IU/L)	40 ± 22	37 ± 15	0.824
Prothrombin time (n = 24, %)	90 ± 19	68 ± 18	0.017
ICG R15 (n = 20, %)	24.3 ± 15.0	30.6 ± 14.2	0.285
K-ICG (n = 20)	0.110 ± 0.033	0.092 ± 0.047	0.165

IU: International units; ICG: Indocyanine green; ICG R15: Indocyanine green retention rate at 15 min; K-ICG: Plasma ICG disappearance rate.

In this series, 20 patients underwent the ICG test to evaluate hepatic functional reserve. Eleven patients had K-ICGs higher than 0.1 and 9 had K-ICGs lower than 0.1. K-ICG was not associated with postoperative complications: there were 8 patients (72.7%) in the high K-ICG group and 2 (22.2%) in the low K-ICG group ($P = 0.07$). As regards intractable ascites, no significant difference was found between the two groups: there were 3 patients (27.2%) in the high K-ICG group and 1 patient (11.1%) in the low K-ICG group ($P = 0.591$).

Eight patients underwent a D2 or D3 lymph node dissection. Of the 8 patients, 3 (37.5%) had postoperative complications. However, in the 17 patients who underwent a D0 or D1 lymph node dissection, 10 (58.8%) had postoperative complications. No significant association was found between the extent of dissection and postoperative complications in this series ($P = 0.411$). For intractable ascites, no significant difference was found between the two groups: there was 1 patient (12.5%) in the D2 or D3 dissection group and 3 patients (27.2%) in the D0 or D1 dissection group ($P > 0.999$).

Of the 3 patients who developed hepatic failure, one died of multiple organ failure on postoperative day 11. This patient had undergone a total gastrectomy with splenectomy, caudal pancreatectomy, and lower esophagectomy for advanced GC with esophageal invasion. Severity of LC of the patient was grade A using the Child-Pugh classification, the K-ICG value was 0.090 and the ICG R15 rate was 29.3%.

Treatment for liver diseases

Of the 25 patients, 12 patients had preoperative esophageal varices. Three of these 12 patients underwent a portosystemic shunt operation. Two underwent a left gastric vein - inferior vena cava shunt operation (Inokuchi shunt[11]) and one an inferior mesenteric- left renal vein shunt operation, in combination with a gastrectomy due to severe varices. In these 3 patients, varices were in remission or stable after surgery. Although the remaining 9 patients did not undergo a shunt operation simultaneously, one patient showed worsened varices and underwent a

Table 2 Clinicopathological characteristics of 25 GC patients with LC using the Child-Pugh classification

	Grade A (*n* = 15)	Grade B (*n* = 10)	*P* value
Cause of cirrhosis			
Alcohol	9	3	0.369
Virus	5	6	
HCV-related	5	4	
HBV-related	0	1	
Both	0	1	
Unknown	1	1	
Preoperative esophageal varices	5	7	0.111
Intraoperative ascites	0	6	0.001
Extent of gastric resection			
Distal	7	5	0.517
Total	7	3	
Wedge	1	2	
Extent of lymph node dissection			
D0	2	3	0.627
D1 (modified gastrectomy A)	8 (6)	4 (4)	
D2	4	3	
D3	1	0	
Residual tumor			
R0	15	10	> 0.999
R1/2	0	0	
Depth of invasion			
pT1	9	7	0.407
pT2	5	2	
pT3	1	1	
Lymph node metastasis			
pN0	11	6	0.758
pN1	1	1	
pN2	1	1	
pN3	1	0	
pNX[1]	1	2	

[1]Histological examination of a regional lymphadenectomy specimen includes 14 or less lymph nodes. Depth of invasion, lymph node metastasis, extent of lymph node dissection were recorded in accordance with the Japanese Classification of Gastric Carcinoma. GC: Gastric cancer; LC: Liver cirrhosis; HBV: Hepatitis B virus; HCV: Hepatitis C virus. R0: No residual tumor; R1: Microscopic residual tumor; R2: Macroscopic residual tumor.

shunt operation 33 mo after gastrectomy.

There were 3 patients who had synchronous solitary HCC in this study. One grade A patient with a tumor 2.5 cm in diameter received intra- and postoperative percutaneous ethanol injection (PEI); one grade B patient with a tumor 1.5 cm in diameter underwent combined procedures, including intraoperative radiofrequency ablation (RFA), postoperative PEI, and transarterial embolization (TAE); and the other grade B patient with HCC 1.8 cm in diameter declined to undergo any treatment.

A total of 2 grade A patients developed metachronous solitary HCC after gastrectomy. The intervals between gastric cancer surgery and diagnosis of HCC in the 2 patients were 54 and 113 mo. One patient underwent PEI and TAE and the treatment for the other patient is unknown. The clinicopathological characteristics of the 5 patients with HCC are summarized in Table 4.

Prognosis

Overall 5-year survival rate for all patients was 49.6%: 58.9% for patients with early GC and 33.3% for patients with advanced GC. Median survival time was 53 and 26 mo respectively (Figure 1A, $P = 0.230$). GC-specific 5-year survival rate for patients with early GC was 90.0%, while that for patients with advanced GC was 58.3% (Figure 1B, $P = 0.010$). Comparing grades A and B using the Child-Pugh classification, overall 5-year survival rate for grade A patients was 60.0% and 30.5% for grade B patients with the median survival time of 59 and 23 mo respectively (Figure 1C, $P = 0.089$).

Table 3 Intra- and postoperative surgical results using the Child-Pugh classification *n* (%)

	Grade A (*n* = 15)	Grade B (*n* = 10)	*P* value
Mean operative blood loss (range, mL)	754 (79-2705)	1103 (182-3073)	0.336
Perioperative transfusion of PRBC	5 (33.3)	6 (60.0)	0.241
Mean volume of transfused PRBC (range, mL)	208 (0-1040)	416 (0-1040)	0.198
Perioperative transfusion of FFP	12 (80.0)	6 (60.0)	0.378
Mean volume of transfused FFP (range, mL)	1904 (0-7760)	2968 (0-10 000)	0.575
Morbidity	7 (46.7)	6 (60.0)	0.688
Ascites	1 (6.7)	4 (40.0)	0.041
Intraabdominal infection	0	2 (20.0)	0.071
Hepatic failure	3 (20.0)	0	0.132
Leakage	2 (13.3)	0	0.229
Sepsis	1 (6.7)	0	0.405
Mortality	1 (6.7)[1]	0	0.405
Median postoperative hospital stay (range, d)	34 (12-63)	29 (12-41)	0.322

[1]Mortality was due to hepatic failure. PRBC: Packed red blood cells; FFP: Fresh frozen plasma.

At the time of writing, 16 of the 25 patients died after GC surgery. The causes of death, excluding one postoperative mortality due to hepatic failure, were as follows: GC in 5 patients; HCC in 4; and 1 for each of the following: lung cancer, cerebral infarction, pneumonia, chronic heart failure, accident, and unknown cause. There were no deaths from chronic hepatic failure or fatal gastrointestinal hemorrhage due to ruptured esophagogastric varices.

The most common cause of death was GC recurrence in patients with advanced GC (4 of 7 deaths) and HCC in patients with early GC (4 of 9 deaths). All of the 4 deaths from HCC were in patients with early GC. Two patients who had synchronous solitary HCC died of HCC within 5 years after the gastrectomy (Table 4).

DISCUSSION

The assessment of perioperative risk of LC is a surgically important issue. In this study, GC patients with LC were divided into two groups according to the Child-Pugh classification and the perioperative outcome was analyzed. Of the 25 patients, 15 were classified as grade A and 10 as grade B. The one case of postoperative mortality in

Table 4 Clinicopathological characteristics of GC patients with HCC

Age (yr)	C-P	pT	pN	Surgery for gastric cancer	HCC	Treatment for HCC	Cause of death	Survival time (mo)
71	Grade A	pT1	pNX	Wedge resection, D0	SYN	PEI	HCC	22
62	Grade A	pT1	pN0	Distal GR, D2	MET	PEI, TAE	HCC	80
55	Grade A	pT1	pN0	Distal GR, D1	MET	Unknown	HCC	121
68	Grade B	pT1	pN0	Distal GR, D1	SYN	RFA, PEI, TAE	Alive	64
81	Grade B	pT1	pN0	Distal GR, D1	SYN	None	HCC	46

C-P: Child-Pugh classification; HCC: Hepatocellular carcinoma; SYN: Synchronous; MET: Metachronous; GR: Gastrectomy; PEI: Percutaneous ethanol injection; TAE: Transarterial embolization; RFA: Radiofrequency ablation.

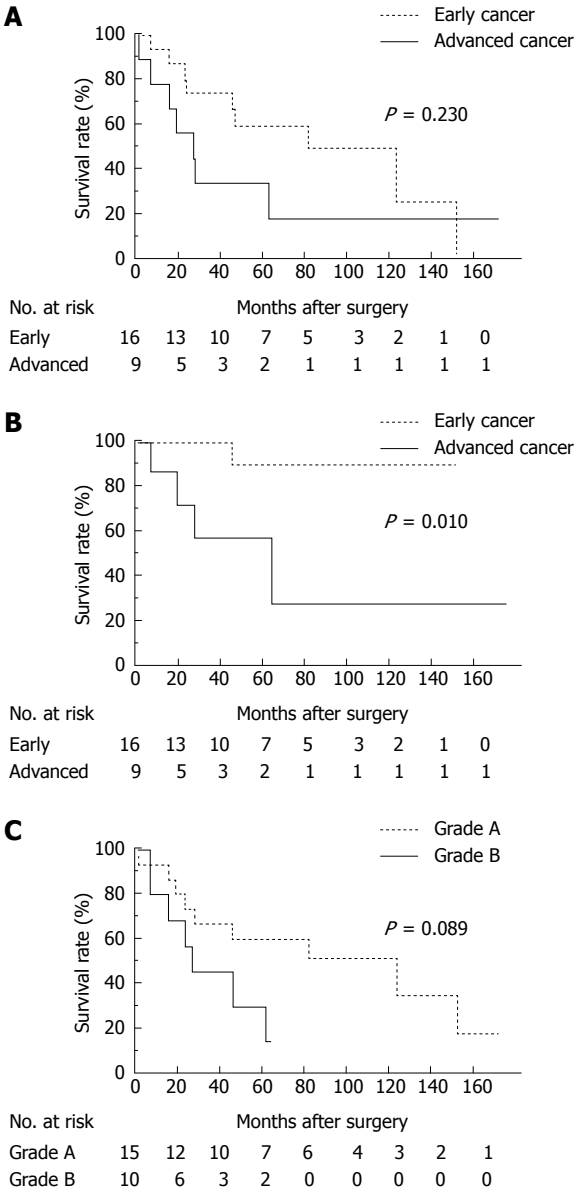


Figure 1 Kaplan-Meier estimates of 25 gastric cancer (GC) patients with liver cirrhosis (LC). A: Overall survival was not significantly different between early and advanced GC patients (overall 5-year survival rates: 58.9% and 33.3% respectively; $P = 0.230$); B: GC-specific survival was significantly higher in early GC patients than in advanced GC patients (5-year survival rates: 90.0% and 58.3% respectively; $P = 0.010$); C: Overall survival using the Child-Pugh classification. The overall 5-year survival rate of grade A patients was 60.0% and those of grade B patients was 30.5% ($P = 0.089$).

this series involved a patient with an advanced GC located in the upper and middle stomach who underwent total gastrectomy, splenectomy, and caudal pancreatectomy together with a D2 dissection including the dissection around the hepatoduodenal ligament. The patient developed postoperative hepatic failure and subsequently multiple organ failure, and died on postoperative day 11. The Child-Pugh score of this patient was 5 and LC was grade A. With respect to complications from surgery, the incidence was generally high: 46.7% in grade A patients and 60.0% in grade B patients. However, there was no significant statistical difference in these two groups and these results show the limitation of risk assessment of GC surgery using the Child-Pugh classification. Conversely, even for grade B patients, radical GC surgery can be performed safely if the surgeon selects the appropriate surgical procedure and prudent care is given to the patient postoperatively. Very recently, Jang *et al*[8] reported the surgical outcomes of 57 GC patients with LC who underwent a radical gastrectomy in 3 university hospitals in South Korea. The Child-Pugh classification system was used for the surgical risk assessment. Operative mortality was noted in only 2 (4.3%) of 46 GC patients with grade A cirrhosis, while it occurred in 3 (27.3%) of 11 GC patients with grade B/C cirrhosis, a significantly larger number than that of grade A patients. In addition, Isozaki *et al*[6] reported that 4 of 26 GC patients with grade B/C cirrhosis based on the Child classification developed serious complications after GC surgery, and 2 (8.0%) died of complications from renal failure and hepatic failure. The mortality rate of grade B cirrhosis patients who underwent GC surgery varies greatly by investigator, possibly because of the paucity of cases analyzed. Clinical studies on GC surgery of patients with grade B or higher LC are very few: there are only five studies[5,6,8,12] including this one, that have analyzed 10 patients or more. To obtain reliable data on operative mortality, an event with very low incidence, analysis of a large patient population based on a nationwide investigation is needed.

This study showed no significant difference in the incidence of overall postoperative complications between grade A and grade B GC patients. However, the development of postoperative intractable ascites was significantly more frequent in grade B patients. All earlier studies showed that, in GC surgery of patients with LC, the incidence of intractable ascites is high, which is clinically important in relation to the extent of lymph node dissection in GC. Lee *et al*[12] reported the surgical outcome of 94 GC patients with LC who underwent a gastrectomy with a D2 lymph node dissection. Two

patients classified as grade B or C according to the Child classification died of postoperative complications from hepatorenal failure with intractable ascites. No serious complications or operative mortality was noted in 82 patients who were classified as grade A. In these patients, ascites was also the common postoperative complication but was well controlled by medication and/or paracentesis. Therefore, Lee *et al*[12] concluded that the presence of compensated cirrhosis, such as grade A, was not a contraindication to a gastrectomy with a D2 or more lymph node dissection. Ryu *et al*[13] reported the surgical outcome of 26 GC patients with LC classified as grade A using the Child-Pugh classification. They found no serious complications or operative mortality although 8 patients received diuretics and one required abdominocentesis. In their series, 25 of the 26 patients underwent a D2 lymph node dissection. Based on these findings, Ryu *et al*[13] claimed that a D2 lymph node dissection could be safely applied to GC patients with low-grade LC, such as a grade A. Jang *et al*[8] concluded that a D2 lymph node dissection in grade B patients should be avoided because they found that in patients undergoing a D2 dissection, none of the grade A patients had developed massive ascites postoperatively, while 3 of 4 grade B patients developed massive ascites. Also, Isozaki *et al*[6] reported 3 in-hospital deaths among 19 GC patients with LC who underwent D2 or more extensive dissection. Of note was that 2 of the 3 patients died of organ failure following the development of significant ascites that was caused by dissection around the hepatoduodenal ligament, as in the one case of death in this series. In this study, 4 of 5 patients who had developed intractable ascites were grade B patients: 3 patients underwent a D0 or D1 dissection; one patient underwent a D2 dissection. Collectively, with regard to the extent of lymph node dissection in LC patients, a D2 dissection should be avoided in grade B patients. In addition, the hepatoduodenal ligament should be kept intact as much as possible, even in grade A patients.

It is widely known that the prognosis of GC patients with LC is poor. Nevertheless, it is essential to have more detailed information on the degree and the cause to establish a better therapeutic strategy. This study showed that the overall 5-year survival rate of early GC patients with LC was as low as 58.9% and that of advanced GC 33.3%, agreeing with previous studies[6,8]. In particular, the prognosis of patients with early GC worsened dramatically, which is markedly different from the overall 5-year survival rate of 93.4% after surgery for T1 tumor based on the nationwide data collected by the Japanese Gastric Cancer Association[10]. The primary cause of this difference was the high mortality related to LC, especially death from HCC. Of the 25 GC patients with LC in this study, 16 had died to date. Four died of liver cancer, similar to the 5 who died of recurrent GC. In this study, in addition to overall survival analysis, GC-specific survival was analyzed in which death due to other diseases was dealt with by censoring. This analytical procedure helps understand the impact of LC-related death on patient survival more clearly. Furthermore, it is noteworthy that all the 5 patients who developed HCC in this study were those with early GC. In this study, nonsurgical therapy was selected for 3 GC patients with synchronous HCC and all of them finally died of HCC. This suggests that a more radical treatment for the HCC should have been chosen even if GC surgery was downscaled or completely omitted. Moreover, it becomes more important to discover metachronous HCC that develops during postoperative follow-up because essentially early GC patients can survive longer. In this study, 2 of 25 patients (8.0%) suffered from metachronous HCC following a gastrectomy. The incidence was very similar to the incidence of 8.5% (3/35) reported by Isozaki *et al*[6] The cumulative appearance rates of HCC were 18.9% and 39.5% at 5 years in HBsAg and anti-HCV-positive cirrhotic patients respectively, both of which are considerably high in Japan[14]. Although this may not be applicable to Western countries where alcoholic cirrhosis is more prevalent and the incidence of liver cancer is low, early detection of HCC is vital during patient follow-up in East Asian countries where the incidences of both GC and HCC are high.

In conclusion, radical gastrectomy can be conducted safely in GC patients with grade B cirrhosis based on the Child-Pugh classification. However, the extent of lymph node dissection should be minimized because grade B patients are at risk of postoperative intractable ascites. The prognosis of GC patients with LC is poor due to HCC. To improve patient prognosis, high-quality control and early diagnosis of HCC by intensive follow-up are vital.

COMMENTS

Background

It remains uncertain whether or not the Child-Pugh classification is sufficiently reliable to assess the risk of gastric cancer (GC) surgery as only a limited number of studies have been conducted. In addition, it is necessary to know the effects of liver cirrhosis (LC)-related diseases, namely hepatocellular carcinoma (HCC), on the prognosis of patients after GC surgery.

Research frontiers

With regard to the extent of lymph node dissection in LC patients, a D2 dissection is controversial. It is essential to have more detailed information about the prognosis of GC patients with LC to establish a better therapeutic strategy.

Innovations and breakthroughs

Clinical outcomes including postoperative morbidity and survival were retrospectively analyzed based on medical records and surgical files. Radical gastrectomy can be conducted safely in GC patients with grade B cirrhosis based on the Child-Pugh classification. However, the extent of lymph node dissection should be minimized because grade B patients are at risk of postoperative intractable ascites. The prognosis of GC patients with LC is poor due to HCC. To improve patient prognosis, high-quality control and early diagnosis of HCC by intensive follow-up are vital.

Applications

The study results suggest that the risk of postoperative intractable ascites is high, particularly in grade B patients. Early detection and complete control of HCC is vital to improve a patient's prognosis.

Terminology

The Child-Pugh classification replaces assessment factors with laboratory data and scores them, and is more frequently used to evaluate overall hepatic function. Prothrombin time is added to replace the nutritional assessment as a modification of the Child's classification.

Peer review

This is a good study in which the authors report on the usefulness of risk assessment of GC surgery based on the currently used Child-Pugh classification. By investigating in detail the prognosis of patients, this report first demonstrates the effects of LC and LC-related diseases on the long-term prognosis of patients with GC.

REFERENCES

1 **Garrison RN**, Cryer HM, Howard DA, Polk HC Jr. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. *Ann Surg* 1984; **199**: 648-655

2 **Fekete F**, Belghiti J, Cherqui D, Langonnet F, Gayet B. Results of esophagogastrectomy for carcinoma in cirrhotic patients. A series of 23 consecutive patients. *Ann Surg* 1987; **206**: 74-78

3 **Sirinek KR**, Burk RR, Brown M, Levine BA. Improving survival in patients with cirrhosis undergoing major abdominal operations. *Arch Surg* 1987; **122**: 271-273

4 **Jakab F**, Ráth Z, Sugár I, Ledniczky G, Faller J. Complications following major abdominal surgery in cirrhotic patients. *Hepatogastroenterology* 1993; **40**: 176-179

5 **Takeda J**, Hashimoto K, Tanaka T, Koufuji K, Kakegawa T. Review of operative indication and prognosis in gastric cancer with hepatic cirrhosis. *Hepatogastroenterology* 1992; **39**: 433-436

6 **Isozaki H**, Okajima K, Kawashima Y, Yamada S, Morita S, Nakajima T, Nakata E, Iga C, Ishibashi T, Tanimura M, Hara H. Optimal extent of lymph node dissection in the surgical treatment of gastric cancer accompanied by liver cirrhosis (in Japanese with English abstract). *Nippon Shokaki Geka Gakkai Zasshi* (Jpn J Gastroenterol Surg) 1991; **24**: 798-804

7 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649

8 **Jang HJ**, Kim JH, Song HH, Woo KH, Kim M, Kae SH, Lee J, Cho JW, Kang JH, Lee SI, Gong SJ, Lee JA, Zang DY. Clinical outcomes of patients with liver cirrhosis who underwent curative surgery for gastric cancer: a retrospective multi-center study. *Dig Dis Sci* 2008; **53**: 399-404

9 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma. 13th ed. Tokyo: Kanehara, 1999

10 **Japanese Gastric Cancer Association**. Gastric cancer treatment guideline. 2nd ed. Tokyo: Kanehara, 2004

11 **Inokuchi K**. A selective portacaval shunt. *Lancet* 1968; **2**: 51-52

12 **Lee JH**, Kim J, Cheong JH, Hyung WJ, Choi SH, Noh SH. Gastric cancer surgery in cirrhotic patients: result of gastrectomy with D2 lymph node dissection. *World J Gastroenterol* 2005; **11**: 4623-4627

13 **Ryu KW**, Lee JH, Kim YW, Park JW, Bae JM. Management of ascites after radical surgery in gastric cancer patients with liver cirrhosis and minimal hepatic dysfunction. *World J Surg* 2005; **29**: 653-656

14 **Ishikawa T**, Ichida T, Yamagiwa S, Sugahara S, Uehara K, Okoshi S, Asakura H. High viral loads, serum alanine aminotransferase and gender are predictive factors for the development of hepatocellular carcinoma from viral compensated liver cirrhosis. *J Gastroenterol Hepatol* 2001; **16**: 1274-1281

S- Editor Li LF **L- Editor** Roemmele A **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.56

World J Gastrointest Surg 2009 November 30; 1(1): 56-58
ISSN 1948-9366 (online)

BRIEF ARTICLE

Gastrointestinal symptomatic outcomes of laparoscopic and open gastrectomy

Bilal Kharbutli, Vic Velanovich

Bilal Kharbutli, Vic Velanovich, Division of General Surgery, Henry Ford Hospital, Detroit, MI 48202, United States
Author contributions: Kharbutli B performed and Velanovich V supervised data collection, review of medical records and literature review; Kharbutli B and Velanovich V co-performed statistical analysis and co-wrote the abstract and manuscript.
Correspondence to: Vic Velanovich, MD, Division of General Surgery, K-8, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202, United States. vvelano1@hfhs.org
Telephone: +1-313-9168984 Fax: +1-313-9167354
Received: July 24, 2009 Revised: August 25, 2009
Accepted: September 2, 2009
Published online: November 30, 2009

Abstract

AIM: To compare the laparoscopic and the open gastrectomy approaches for short term morbidity, length of hospital stay and also long term gastrointestinal symptoms.

METHODS: Patients who have undergone gastrectomy had their medical records reviewed for demographic data, type of gastrectomy, short term morbidity, and length of hospital stay. Patients were contacted and asked to complete the Gastrointestinal Symptom Rating Scale (GSRS). The GSRS measures three domains of GI symptoms: Dyspepsia Syndrome (DS) for the foregut (best score 0, worse score 15), indigestion syndrome (IS) for the midgut (best score 0, worse score 12), and bowel dysfunction syndrome (BDS) for the hindgut (best score 0, worse score 16). Statistical analysis was done using the Mann-Whitney *U*-test.

RESULTS: We had complete data on 32 patients: 7 laparoscopic and 25 open. Of these, 25 had a gastroenteric anastomosis and 6 did not. The table shows the results as medians with interquartile range. Laparoscopic gastrectomy had a better score than open gastrectomy in the DS domain (0 *vs* 1, $P = 0.02$), while gastrectomy without anastomosis had a better score than gastrectomy with anastomosis in the IS domain (0 *vs* 1, $P = 0.05$).

CONCLUSION: Patients have little adverse gastrointestinal symptoms and preserve good gastrointestinal function after undergoing any type of gastrectomy. Laparoscopic approach had better dyspepsia and foregut symptoms. Performing an anastomosis led to mild adverse midgut and indigestion effects

Key words: Laparoscopic; Gastrectomy; Symptomatic outcomes; Gastric tumor; Open gastrectomy; Laparoscopic gastrectomy

Peer reviewer: Lee H Bouwman, MD, PhD, MSc, Surgery Department, Bronovo Hospital, Bronovolaan 5, 2597 AX The Hague, The Netherlands

Kharbutli B, Velanovich V. Gastrointestinal symptomatic outcomes of laparoscopic and open gastrectomy. *World J Gastrointest Surg* 2009; 1(1): 56-58 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/56.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.56

INTRODUCTION

Gastrectomy is the most effective treatment for a variety of gastric pathologies, both benign and malignant, nevertheless it may lead to significant short and long term gastrointestinal symptoms in addition to an associated procedural morbidity and mortality. As minimally invasive surgery has advanced, laparoscopic gastrectomy is advocated as a treatment method for the different gastric pathologies with equivalent pathologic results, faster recovery, shorter length of stay, lower morbidity and earlier return of bowel function[1-14].

There have been many published studies that compare laparoscopic and open gastrectomy in regards to post operative morbidity and mortality, length of hospital stay and surgical resection adequacy for benign and malignant pathologies. Little data exist that evaluate gastrointestinal symptomatology after either laparoscopic or open

gastrectomy using objective and validated instruments such as the gastrointestinal symptom rating scale.

This study compares the laparoscopic and the open gastrectomy for short term morbidity, length of hospital stay and also long term gastrointestinal symptomatology and compares results to those published in the literature.

MATERIALS AND METHODS

Patients who had undergone elective gastrectomy for benign and malignant pathologies at our institution had their medical records reviewed for demographic data, type of gastrectomy, and short term morbidity, and length of hospital stay. Patients who had emergent surgery or combined procedures performed were excluded from the study.

Patients were contacted and asked to complete the Gastrointestinal Symptom Rating Scale (GSRS). The GSRS measures three domains of GI symptoms: Dyspepsia Syndrome (DS) assesses foregut symptomatology (best score 0, worse score 15), Indigestion syndrome (IS) for the midgut symptomatology (best score 0, worse score 12) and Bowel dysfunction syndrome (BDS) for the hindgut (best score 0, worse score 16).

Statistical analysis was done using the Mann-Whitney *U*-test.

RESULTS

We had complete data on 32 patients: 7 laparoscopic and 25 open. Of these, 23 had a gastroenteric anastomosis and 9 did not, (Table 1). We compared the length of stay between patients who underwent open and laparoscopic gastrectomy, (Table 2) and also between those who did and did not have gastroenteric anastomosis with their gastrectomy, (Table 3).

The results showed that patients who had laparoscopic gastrectomy had a shorter length of hospital stay (mean 5 d) compared to open gastrectomy (mean 9.6 d), (Table 2). These results are comparable to other published studies[2,6,8,9,12-18].

Table 3 shows that those who had a gastroenteric anastomosis performed with gastrectomy had longer length of hospital stay (Mean 9.8 d) compared to those who did not (mean 5.3 d). Delay in return of bowel function was the main reason behind the prolonged hospital stay.

Median follow up was 37 mo for the open group and 29 mo for the laparoscopic group. Median age was 69 years for the open group and 73 years for the laparoscopic group. Neither comparison was statistically significant, (Table 4). We also noted that the length of time after operation did not seem to affect severity of GI symptoms.

With respect to gastrointestinal symptoms as measured by the GSRS. The comparison revealed that there is a small but statistically significant difference between patients who had open gastrectomy compared to those who had laparoscopic gastrectomy only in the DS Domain with more symptoms in open gastrectomy patients in that domain but not in the two other domains, (Table 5).

There was also a small but statistically significant difference between patients who had gastrectomy with an anastomosis and those who did not have a gastroenteric anastomosis in the IS Domain with patients who had the anastomosis having more symptoms. There was no statistically significant difference in the two other domains between these two groups, (Table 6).

Total morbidity rate was approximately 40% in the open gastrectomy group including 16% wound complications (SSI, Hernia); four patients (16%) with gastrointestinal obstruction, one with post operative MI and one patient with pneumonia. The postoperative morbidity rate in the laparoscopic group was 28%; (one patient had UTI and another had urinary retention with acute renal failure), with no wound complications. These morbidity data were equivalent to that published in the literature[1,3,6,8,11-13,16,17].

Table 1 Distribution of patients

	w/ anastomosis	w/o anastomosis	
Open gastrectomy	21	4	25
Laparoscopic gastrectomy	2	5	7
	23	9	32

Table 2 Comparison of length of stay between open and laparoscopic gastrectomy

Length of stay	Median/mean in days	*P*
Open gastrectomy (*n* = 25)	7/9.6	
Laparoscopic gastrectomy (*n* = 7)	4/5	0.0026

Table 3 Comparison of length of stay between gastrectomy w/ and w/o anastomosis

Length of stay	Median/mean in days	*P*
Gastrectomy w/ anastomosis (*n* = 23)	8/9.8	
Gastrectomy w/o anastomosis (*n* = 9)	5/5.3	0.0007

Table 4 Comparison of age and follow up between open and laparoscopic gastrectomy

	Median age in years	Median follow up in months
Open gastrectomy (*n* = 25)	69	37
Laparoscopic gastrectomy (*n* = 7)	73	29
P	NS	NS

NS: Not significant.

DISCUSSION

Overall, patients have relatively few adverse gastrointestinal symptoms in any of the GSRS domains after both open and laparoscopic gastrectomies, whether or not a gastroenteric anastomosis was performed. This implies that most patients return to relatively good gastrointestinal function after gastrectomy. Patients with laparoscopic gastrectomy had a slightly better median score in the DS domain compared to the open technique, while patients who had gastrectomy without an anastomosis had a

Table 5 Median GSRS scores (with interquartile range) for open and laparoscopic gastrectomy

GSRS domain	Open gastrectomy	Laparoscopic gastrectomy	*P* value
Dyspepsia syndrome	1 (0-3)	0 (0-3)	0.02
Indigestion syndrome	1 (0-2)	0 (0-2)	NS
Bowel dysfunction syndrome	2 (1-4)	1 (0-4)	NS

GSRS: Gastrointestinal Symptom Rating Scale.

Table 6 Median GSRS scores (with interquartile range) for gastrectomy w/ and w/o anastomosis

GSRS domain	Partial gastrectomy w/ anastomosis	Partial gastrectomy w/o anastomosis	*P* value
Dyspepsia syndrome	1 (0-3)	0 (0-1)	NS
Indigestion syndrome	1 (0-4)	0 (0-1)	0.05
Bowel dysfunction syndrome	2 (1-4)	1 (0-1)	NS

better median score in the IS domain implying that an anastomosis had mild adverse midgut effects.

Performing open gastrectomy resulted in longer length of hospital stay and greater wound complications compared to laparoscopic gastrectomy. While performing gastroenteric anastomosis lead to slightly more Indigestion Symptomatology and longer hospital stay compared to gastrectomies without anastomosis.

These data reflect advantages for laparoscopic gastrectomy and increased midgut symptoms, albeit minor, for gastroenteric anastomosis. The results of this study will be valuable for surgeons counseling patients on the long-term effects of these operations on their quality of life.

COMMENTS

Background

Gastrectomy is the most effective treatment for a variety of gastric tumors. This study compares different aspects comparing the two most commonly used gastrectomy methods, open *vs* laparoscopic.

Research frontiers

Gastrectomy can lead to significant gastrointestinal symptoms. As minimally invasive surgery has advanced, laparoscopic gastrectomy is advocated as a treatment method with equivalent pathologic results, with faster recovery.

Innovations and breakthroughs

Very little data using objective, validated instruments of gastrointestinal symptoms to compare laparoscopic and open gastrectomy exist. This study compares the two methods using the Gastrointestinal Symptomatic Rating Scale (GSRS) as an objective instrument. It also compares other aspects of post operative course.

Applications

Having a better understanding of, and objective data for the comparison between the outcomes of these common gastrectomy methods will aid physicians and patients in clinical discussion and decision making.

Terminology

Gastrectomy or gastric resection is a surgical procedure for stomach resection due to variable benign and malignant causes including peptic ulcers and tumors. Laparoscopic Surgery is a minimally invasive procedure that involves the use of ports, camera and smaller incisions.

Peer review

The authors compared gastrointestinal symptomatic outcomes of laparoscopic and open gastrectomy. They found that patients have relatively little adverse gastrointestinal symptoms in any of the types of gastrectomies in any of the GSRS domains. This paper is well written and easy to read.

REFERENCES

1 **Huscher CG**, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A, Ponzano C. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Ann Surg* 2005; **241**: 232-237

2 **Reyes CD**, Weber KJ, Gagner M, Divino CM. Laparoscopic vs open gastrectomy. A retrospective review. *Surg Endosc* 2001; **15**: 928-931

3 **Dulucq JL**, Wintringer P, Perissat J, Mahajna A. Completely laparoscopic total and partial gastrectomy for benign and malignant diseases: a single institute's prospective analysis. *J Am Coll Surg* 2005; **200**: 191-197

4 **Dulucq JL**, Wintringer P, Stabilini C, Solinas L, Perissat J, Mahajna A. Laparoscopic and open gastric resections for malignant lesions: a prospective comparative study. *Surg Endosc* 2005; **19**: 933-938

5 **Chang HM**, Lee SW, Nomura E, Tanigawa N. Laparoscopic versus open gastrectomy for gastric cancer patients with COPD. *J Surg Oncol* 2009; **100**: 456-458

6 **Varela JE**, Hiyashi M, Nguyen T, Sabio A, Wilson SE, Nguyen NT. Comparison of laparoscopic and open gastrectomy for gastric cancer. *Am J Surg* 2006; **192**: 837-842

7 **Memon MA**, Khan S, Yunus RM, Barr R, Memon B. Meta-analysis of laparoscopic and open distal gastrectomy for gastric carcinoma. *Surg Endosc* 2008; **22**: 1781-1789

8 **Strong VE**, Devaud N, Allen PJ, Gonen M, Brennan MF, Coit D. Laparoscopic versus open subtotal gastrectomy for adenocarcinoma: a case-control study. *Ann Surg Oncol* 2009; **16**: 1507-1513

9 **Francescutti V**, Choy I, Biertho L, Goldsmith CH, Anvari M. Gastrectomy and esophagogastrectomy for proximal and distal gastric lesions: a comparison of open and laparoscopic procedures. *Surg Innov* 2009; **16**: 134-139

10 **Kitano S**, Shiraishi N. Minimally invasive surgery for gastric tumors. *Surg Clin North Am* 2005; **85**: 151-164, xi

11 **Tabrizian P**, Nguyen SQ, Divino CM. Laparoscopic management and longterm outcomes of gastrointestinal stromal tumors. *J Am Coll Surg* 2009; **208**: 80-86

12 **Feliu X**, Besora P, Clavería R, Viñas X, Salazar D, Fernández E. Laparoscopic treatment of gastric tumors. *J Laparoendosc Adv Surg Tech A* 2007; **17**: 147-152

13 **Song KY**, Park CH, Kang HC, Kim JJ, Park SM, Jun KH, Chin HM, Hur H. Is totally laparoscopic gastrectomy less invasive than laparoscopy-assisted gastrectomy?: prospective, multicenter study. *J Gastrointest Surg* 2008; **12**: 1015-1021

14 **Shehzad K**, Mohiuddin K, Nizami S, Sharma H, Khan IM, Memon B, Memon MA. Current status of minimal access surgery for gastric cancer. *Surg Oncol* 2007; **16**: 85-98

15 **Berindoague R**, Targarona EM, Feliu X, Artigas V, Balagué C, Aldeano A, Lahoud A, Navines J, Fernandez-Sallent E, Trias M. Laparoscopic resection of clinically suspected gastric stromal tumors. *Surg Innov* 2006; **13**: 231-237

16 **Rivera RE**, Eagon JC, Soper NJ, Klingensmith ME, Brunt LM. Experience with laparoscopic gastric resection: results and outcomes for 37 cases. *Surg Endosc* 2005; **19**: 1622-1626

17 **Sexton JA**, Pierce RA, Halpin VJ, Eagon JC, Hawkins WG, Linehan DC, Brunt LM, Frisella MM, Matthews BD. Laparoscopic gastric resection for gastrointestinal stromal tumors. *Surg Endosc* 2008; **22**: 2583-2587

18 **Liew V**, Taylor C, Ghusn M, Jamnagerwalla M, Layani L. Laparoscopic gastric resection for benign and malignant conditions: lessons learned from 35 consecutive cases. *ANZ J Surg* 2007; **77**: 787-791

S- Editor Li LF **L- Editor** Lalor PF **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.59

World J Gastrointest Surg 2009 November 30; 1(1): 59-61
ISSN 1948-9366 (online)

CASE REPORT

Peroral cholangioscopy-assisted guidewire placement for removal of impacted stones in the cystic duct remnant

Mansour A Parsi

Mansour A Parsi, Center for Endoscopy and Pancreatobiliary Disorders, Digestive Disease Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, United States
Author contributions: Parsi MA contributed entirely to this case report.
Correspondence to: Mansour A Parsi, MD, Center for Endoscopy and Pancreatobiliary Disorders, Digestive Disease Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, United States. parsim@ccf.org
Telephone: +1-216-4454880 Fax: +1-216-4446284
Received: May 27, 2009 Revised: July 19, 2009
Accepted: July 26, 2009
Published online: November 30, 2009

Abstract

It is well known that impacted biliary stones are difficult to remove endoscopically. Among the many factors associated with failure of endoscopic therapy for removal of bile duct stones, impaction ranks high. One of the reasons behind failure of endoscopic therapy in such cases is that the impacted stone often does not allow passage of a guidewire. Recent introduction of a novel single-operator cholangioscopy system has made it possible for a single endoscopist to use cholangioscopy for evaluation and treatment of a wide variety of biliary disorders. This cholangioscopy system was used for placement of a guidewire in the cystic duct remnant with subsequent removal of an impacted stone which had prevented passage of a guidewire by conventional means.

Key words: Endoscopic retrograde cholangiopancreatography; Cholangioscopy; Guidewire; Choledocholithiasis; Cystic duct; Cystic duct remnant

Peer reviewers: Dr. Jean L Frossard, Division of Gastroenterology, Geneva University Hospital, Rue Micheli du Crest, 1211 Geneva 14, Switzerland; Beata Jolanta Jabłońska, MD, PhD, Department of Digestive Tract Surgery, University Hospital of the Medical University of Silesia, Medyków 14 St. 40-752 Katowice, Poland

Parsi MA. Peroral cholangioscopy-assisted guidewire placement for removal of impacted stones in the cystic duct remnant. *World J Gastrointest Surg* 2009; 1(1): 59-61 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/59.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.59

INTRODUCTION

Choledocholithiasis is a common condition[1-5]. Most bile duct stones can be effectively removed by endoscopic retrograde cholangiopancreatography (ERCP)[6]. In the vast majority of cases, this is achieved after placement of a guidewire which is then used to guide instruments such as lithotripsy baskets or extraction balloons. Occasionally, when a stone is impacted, placement of a guidewire in the desired location cannot be accomplished, and more invasive procedures such as transhepatic access or surgery may become necessary. In this report, we describe a new technique for successful guidewire placement for subsequent treatment and removal of impacted stones after failed placement by conventional means.

CASE REPORT

A 64 year-old-man with a remote history of cholecystectomy was referred for ERCP for treatment of choledocholithiasis. The cholangiogram showed stones in the common hepatic duct and the cystic duct remnant (Figure 1). The common hepatic duct stones were easily removed after placement of a guidewire in the common hepatic duct followed by biliary sphincterotomy and balloon extraction. Removal of the stones in the cystic duct, however, proved to be much more challenging. One of the cystic duct stones was impacted at the insertion of the cystic duct to the common bile duct, preventing passage of a guidewire (Jagwire, Boston Scientific, Natick, MA; Figure 1). An extraction balloon which was already

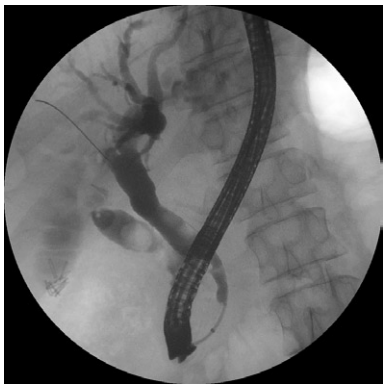


Figure 1 Fluoroscopic image obtained during ERCP showing filling defects (stones) in the common hepatic duct and cystic duct remnant.

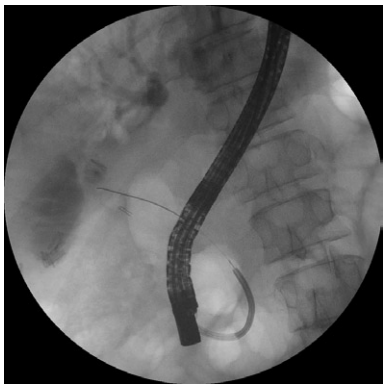


Figure 2 A guidewire is placed in the cystic duct remnant under direct cholangioscopic guidance.

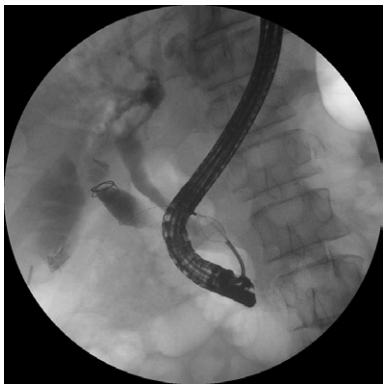


Figure 3 A guidewire is coiled in the cystic duct remnant. A basket passed over the guidewire is holding a large radiolucent (cholesterol) stone for removal.

in place was inflated and the insertion point of the cystic duct was probed with the guidewire while changing the orientation and the degree of inflation of the balloon. The guidewire still would not pass. The balloon was then positioned close to the stone, inflated and slightly pulled down towards the ampulla to straighten and stretch the bile duct while probing with the guidewire was continued[7]. However, this technique also failed to provide access to the cystic duct. The balloon was then exchanged with a rotatable sphincterotome (Autotome Rx, Boston Scientific, Natick, MA). This sphincterotome has a rotating handle which is designed to change the tip orientation to facilitate cannulation. Probing with the guidewire through the sphincterotome at different tip orientations also failed. The guidewire was then exchanged for an angled tip hydrophilic guidewire (Hydra Jagwire, Boston Scientific, Natick, MA) and the sequence described above was repeated without success. After failing to traverse the stone by conventional means, a cholangioscope (SpyGlass Direct Visualization System, Boston Scientific, Natick, MA) was introduced into the bile duct. Through the accessory channel of the cholangioscope, under direct visualization and using low volume saline irrigation, a hydrophilic guidewire was manipulated past the impacted stone and placed in the cystic duct remnant (Figure 2). The cholangioscope was then removed and the stones were extracted using a basket passed over the guidewire (Figure 3).

DISCUSSION

Gallstone disease or cholelithiasis continues to be a major health problem throughout the world, affecting approximately 10%-20% of the Caucasian population[8]. In addition, 15%-20% of patients with gallstone disease also have stones in their biliary ductal system (choledoch olithiasis)[5]. Stones in the biliary ductal system have to be removed because of their potential to cause cholangitis and pancreatitis[6,9,10]. ERCP with biliary sphincterotomy and stone extraction are well-established therapeutic procedures for the treatment of gallstones. Appropriate guidewire placement is a requirement in most ERCP procedures that are performed for gallstone extraction. In most cases, guidewire placement is accomplished easily. In some cases, however, it can represent a time-consuming challenge. Multiple instruments have been developed and several techniques have been described to help with guidewire placement during ERCP. Despite use of different equipment and innovative techniques, a guidewire sometimes can not be placed in the desired location and a more invasive procedure may become necessary.

Recently, a new single-operator cholangioscopy system became available (SpyGlass Direct Visualization System, Boston Scientific, Natick, MA, USA)[11,12]. This system, which consists of re-useable and single use components, allows direct visualization of the biliary tree by a single endoscopist. Its other advantages are a 4-way tip deflection, which allows better access and maneuverability, and 2 dedicated irrigation channels allowing better visualization of intraductal pathology. I and my colleagues have previously reported our experience with this system in the treatment of difficult to remove biliary stones[13], evaluation of indeterminate biliary strictures[14], investigation of "idiopathic" recurrent acute pancreatitis[15] and treatment of anastomotic strictures in liver transplant patients[16]. This study reports the experience of using this device for removal of impacted stones in the cystic duct

remnant. Most symptomatic patients with calculi in the cystic duct remnant undergo laparoscopic re-operation for stone management[17-19]. In this case, this peroral cholangioscopy system was used to place a guidewire in the cystic duct remnant under direct visualization after a failed attempt during ERCP, with subsequent removal of an impacted calculus. This innovative technique allows surgery to be avoided in selected cases.

REFERENCES

1 **Everhart JE**, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology* 1999; **117**: 632-639
2 **Everhart JE**, Yeh F, Lee ET, Hill MC, Fabsitz R, Howard BV, Welty TK. Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. *Hepatology* 2002; **35**: 1507-1512
3 **Aerts R**, Penninckx F. The burden of gallstone disease in Europe. *Aliment Pharmacol Ther* 2003; **18** Suppl 3: 49-53
4 **Festi D**, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A. Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). *World J Gastroenterol* 2008; **14**: 5282-5289
5 **Tazuma S**. Gallstone disease: Epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). *Best Pract Res Clin Gastroenterol* 2006; **20**: 1075-1083
6 **Caddy GR**, Tham TC. Gallstone disease: Symptoms, diagnosis and endoscopic management of common bile duct stones. *Best Pract Res Clin Gastroenterol* 2006; **20**: 1085-1101
7 **Ersoz G**, Tekin F, Ozutemiz O, Tekesin O. A novel technique for biliary strictures that cannot be passed with a guide wire. *Endoscopy* 2007; **39** Suppl 1: E332
8 **Steiner CA**, Bass EB, Talamini MA, Pitt HA, Steinberg EP. Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. *N Engl J Med* 1994; **330**: 403-408
9 **Forsmark CE**, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology* 2007; **132**: 2022-2044
10 **Moreau JA**, Zinsmeister AR, Melton LJ 3rd, DiMagno EP. Gallstone pancreatitis and the effect of cholecystectomy: a population-based cohort study. *Mayo Clin Proc* 1988; **63**: 466-473
11 **Chen YK**, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). *Gastrointest Endosc* 2007; **65**: 832-841
12 **Chen YK**, Parsi MA, Binmoeller KF, Hawes RH, Pleskow D, Slivka A, Haluszka O, Petersen BT, Sherman S, Deviere J, Meisner S, Stevens PD, Costamagna G, Ponchon T, Neuhaus H. Peroral cholangioscopy (PO) using a disposable steerable single operator catheter for biliary stone therapy and assessment of indeterminate strictures - A multicenter experience using Spyglass. *Gastrointest Endosc* 2008; **67**: AB103
13 **Parsi MA**, Neuhaus H, Pleskow D, Binmoeller KF, Hawes RH, Petersen BT, Sherman S, Stevens PD, Deviere J, Haluszka O, Costamagna G, Meisner S, Ponchon T, Slivka A, Chen YK. Peroral Cholangioscopy Guided Stone Therapy - Report of an International Multicenter Registry. *Gastrointest Endosc* 2008; **67**: AB102
14 **Pleskow D**, Parsi MA, Chen YK, Neuhaus H, Slivka A, Haluszka O, Petersen BT, Deviere J, Sherman S, Meisner S, Hawes RH, Stevens PD, Ponchon T, Costamagna G, Binmoeller KF. Biopsy of indeterminate biliary strictures - does direct visualization help? - A multicener experience. *Gastrointest Endosc* 2008; **67**: AB103
15 **Parsi MA**, Sanaka MR, Dumot JA. Iatrogenic recurrent pancreatitis. *Pancreatology* 2007; **7**: 539
16 **Parsi MA**, Guardino J, Vargo JJ. Peroral cholangioscopy-guided stricture therapy in living donor liver transplantation. *Liver Transpl* 2009; **15**: 263-265
17 **Tantia O**, Jain M, Khanna S, Sen B. Post cholecystectomy syndrome: Role of cystic duct stump and re-intervention by laparoscopic surgery. *J Minim Access Surg* 2008; **4**: 71-75
18 **Palanivelu C**, Rangarajan M, Jategaonkar PA, Madankumar MV, Anand NV. Laparoscopic management of remnant cystic duct calculi: a retrospective study. *Ann R Coll Surg Engl* 2009; **91**: 25-29
19 **Lum YW**, House MG, Hayanga AJ, Schweitzer M. Postcholecystectomy syndrome in the laparoscopic era. *J Laparoendosc Adv Surg Tech A* 2006; **16**: 482-485

S- Editor Li LF **L- Editor** Cant MR **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.62

World J Gastrointest Surg 2009 November 30; 1(1): 62-64
ISSN 1948-9366 (online)

CASE REPORT

Actinomycosis of the sigmoid colon: A case report

Antonio Privitera, Charanjit Singh Milkhu, Vivek Datta, Manuel Rodriguez-Justo, Alastair Windsor, Charles Richard Cohen

Antonio Privitera, Charanjit Singh Milkhu, Vivek Datta, Alastair Windsor, Charles Richard Cohen, Department of Surgery, University College London Hospitals, London NW1 2BU, United Kingdom
Manuel Rodriguez-Justo, Histopathology Department, Royal Free & University College Medical School, Rockefeller Building, London WC1E 6JJ, United Kingdom
Author contributions: All authors have participated in the perioperative treatment of the patient, diagnosis and follow-up.
Correspondence to: Dr. Antonio Privitera, MD, PhD, MRCS, Department of Surgery, University College London Hospitals, London NW1 2BU, United Kingdom. privitera@hotmail.com
Telephone: +44-759-5423060 Fax: +44-120-6742030
Received: July 15, 2009 Revised: September 15, 2009
Accepted: September 22, 2009
Published online: November 30, 2009

Key words: Abdominal pain; Actinomycosis; Gram-positive bacteria; Sigmoid colon; Sulfur

Peer reviewers: Walter E Longo, Professor, Department of Surgery, Yale University School of Medicine, 205 Cedar Street, New Haven, CT 06510, United States; Sri P Misra, Professor, Gastroenterology, Moti Lal Nehru Medical College, Allahabad 211001, India

Privitera A, Milkhu CS, Datta V, Rodriguez-Justo M, Windsor A, Cohen CR. Actinomycosis of the sigmoid colon: A case report. *World J Gastrointest Surg* 2009; 1(1): 62-64 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/62.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.62

Abstract

Abdominal actinomycosis is a chronic suppurative infection caused by *Actinomyces* species. The ileo-cecal region is most commonly affected, while the left side of the colon is more rarely involved. The infection has a tendency to infiltrate adjacent tissues and is therefore rarely confined to a single organ. Presentation may vary from non specific symptoms and signs to an acute abdomen. A computed tomography scan is helpful in identifying the inflammatory process and the organs involved. It also allows visual guidance for percutaneous drainage of abscesses, thus aiding diagnosis. Culture is difficult because of the anaerobic character and slow growth of actinomycetes. Colonoscopy is usually normal, but may shows signs of external compression. Preoperative diagnosis is rare and is established only in less than 10% of cases. In uncomplicated disease, high dose antibiotic therapy is the mainstay of treatment. Surgery is often performed because of a difficulty in diagnosis. Surgery and antibiotics are required in the case of complicated disease. Combined medical and surgical treatment achieves a cure in about 90% of cases. The authors report a case of sigmoid actinomycosis where diagnosis was made from the histology, and a review of the literature is presented.

INTRODUCTION

Actinomycosis is a chronic suppurative infection which spreads to contiguous tissues and has the tendency to form external sinuses that may drain characteristic sulfur granules composed of a matrix of calcium phosphate, colonies of actinomycetes, cellular debris and associated organisms[1]. The most common pathogen in humans is *Actinomyces Israelii*, named after Israel who was first to describe the microorganism in a human autopsy specimen[2]. This is a gram-positive, non-spore forming anaerobic bacterium which is a commensal in the mucosa of the oral cavity and upper gastrointestinal tract, but able to cause opportunistic infections[1].

Cervicofacial actinomycosis is the most common clinical form, comprising up to 60% of cases. Abdominal actinomycosis is rare and reported only in about 20% of cases[3].

The authors report a case of actinomycosis of the sigmoid colon and review the literature.

CASE REPORT

A 67-year-old African-Caribbean lady presented with

a 3-mo history of altered bowel habits associated with worsening right iliac fossa pain and nausea. Past medical history showed hypertension, depression and a left-sided stroke. Her surgical history revealed a cesarean section at the age of 25. On examination she was dehydrated, pyrexic (38.2℃) and tachycardic (118 beats/min). The abdomen was tender with guarding in the right iliac fossa, and obstructive bowel sounds were heard. Blood tests showed a microcytic anemia (hemoglobin 9.3 g/dL) and a high white cell count (20 000/mm^3). A rapid sickle cell test performed prior to the procedure was negative.

A computed tomography (CT) scan of the abdomen and pelvis was performed and this showed a 6.5 cm × 7.7 cm inflammatory mass in the right iliac fossa involving the sigmoid colon which contained a few diverticulae. No free air was noted. The patient was resuscitated, transfused with 2 units of blood and was commenced on broad spectrum antibiotics. At laparotomy, an abscessed mass of the sigmoid colon was found. This involved a loop of small bowel and infiltration of the uterus, fallopian tubes and ovaries. A Hartmann's procedure was carried out (Figure 1). Histology showed an inflammatory mass with abscess formation arising from outside the bowel with the mucosa being well defined and unremarkable. The bowel wall was fibrotic and edematous with a few diverticulae, but no evidence of perforation. Numerous lymphoid aggregates, some with reactive germinal centers were present within the submucosa. Extensive pericolic necrosis containing numerous bacterial colonies of *Actinomyces* species were noted (Figures 2 and 3). A diagnosis of sigmoid actinomycosis was made. The patient made an uneventful recovery and was started on a 6-mo course of penicillin. At 1-year follow-up she was well and free from disease.

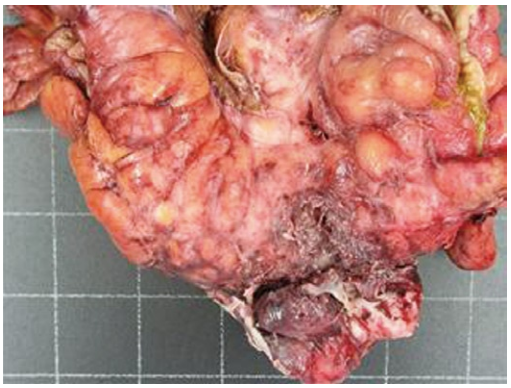


Figure 1 Surgical specimen: Sigmoid colon mass (80 mm × 30 mm) with abscess formation.

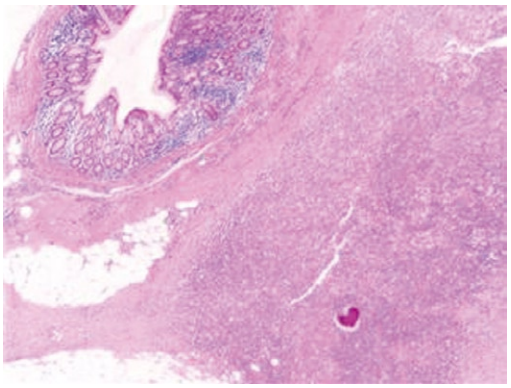


Figure 2 Histology: A colony of Actinomyces is seen within the pericolonic inflammatory tissue.

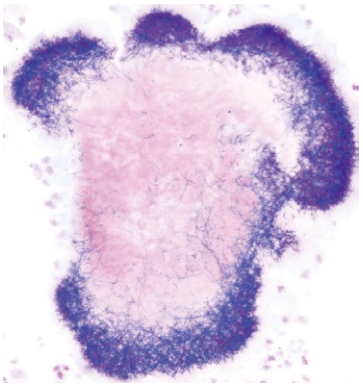


Figure 3 Gram-positive staining of an Actinomyces colony.

DISCUSSION

Actinomycetes are normally not capable of invading the intact intestinal mucosa. However, under certain circumstances deeper invasion occurs. Predisposing factors include immunosuppression (HIV, diabetes), surgical trauma, appendicitis, diverticulitis, bowel perforation, foreign bodies and neoplasia[3-5]. The bacterium is found in up to 25% of cervical smears performed on women with an intrauterine device and this may explain a higher incidence of infection in these patients[6-9]. No predisposing factors are noted in about 50% of cases[10].

Once outside the intestine, the infection usually spreads locally with only a rare incidence of hematogenous or lymphatic spread[11].

The ileo-cecal region is most commonly involved[12]. The left side of the colon is rarely reported to be affected[3,13-20]. Hepatic involvement accounts for 5%-15% of cases and is often associated with multiple small abscesses[21]. Other reported sites include the stomach, gallbladder, pancreas, small bowel, anorectal region, pelvis and abdominal wall[3,5]. Involvement of retroperitoneal organs may result from hematogenous dissemination or direct extension[22,23].

Abdominal actinomycosis usually presents as a slowly growing mass which may be associated with altered bowel habits, nausea, vomiting and cramping pain. Constitutional symptoms are common and include anorexia, weight loss, fever and night sweats. Mild to moderate leukocytosis is often noted[3,11,12]. Occasionally, the disease may be latent for years and manifest itself in the form of multiple sinuses, fistulae, bowel stricture or hydronephrosis[4,5,23].

A preoperative diagnosis is rarely considered and is established only in less than 10% of cases. The nature of the organism is generally identified from a surgically resected specimen, culture from abscesses or at autopsy[3,18].

Radiographic evidence is usually non specific. Barium studies may show signs of external bowel compression with a tapered narrowing of the lumen, but complete

obstruction is rarely seen[6]. Colonoscopy is usually not useful in diagnosis as the disease is of extramucosal origin. However, endoscopy is important to exclude colitis or neoplastic disease and may reveal luminal narrowing or stiffness. Occasionally, nodules with central umbilication are noted and these are related to bowel wall fibrosis as a result of chronic inflammation[19].

A CT scan is helpful in identifying the inflammatory mass and the organs involved. Bowel thickening and inflammatory changes which cross fascial planes and involve multiple compartments are usually seen. CT-guided drainage of abscesses may also lead to identification of the microorganism[19]. Sulfur granules can be observed in the purulent material in 50% of cases, but these are not pathognomonic for the disease. In fact, *Nocardia, Streptomyces*, and some *Staphylococci* can produce comparable granules[24]. Culture is difficult because of the anaerobic characteristics and slow growth of *Actinomyces*. Laboratory tests may reveal a normocytic, normochromic anemia, leukocytosis and an elevated erythrocyte sedimentation rate[25].

Gastrointestinal actinomycosis resembles other chronic inflammatory bowel diseases such as tuberculosis and Crohn's disease, particularly when fistula or sinus tracts are present. Also, bowel malignancy, diverticulitis, appendicitis and amebiasis are part of the differential diagnosis[3]. If a diagnosis can be made without surgery and the disease is uncomplicated, the treatment of choice is an antibiotic. High-dose penicillin is the standard treatment, although cephalosporin is often used as it can be administered on a less frequent dosing schedule. Other effective antibiotics include tetracycline, erythromycin, chloramphenicol, clindamycin and imipenem[3,26-28]. There is still controversy regarding the dosage and duration of antibiotic treatment. However, a long course for a period of at least 6 mo or until disappearance or stabilization of the lesions is recommended, in consideration of the low penetration in the fibrotic area and the tendency of the disease to recur[5,18]. Surgical treatment is often required because of difficulty in diagnosis or in combination with antibiotics in the presence of extensive disease, necrosis, abscess, stricture or persisting sinuses and fistulae. Combined medical and surgical treatment achieves a cure in about 90% of cases[19].

In conclusion, abdominal actinomycosis is to be considered in the differential diagnosis of an abdominal mass. Predisposing factors, imaging, blood tests and microbiology studies may aid diagnosis. Medical treatment should be tried first in uncomplicated cases and surgery limited to dealing with complications or persistent disease.

REFERENCES

1 **Brown JR**. Human actinomycosis. A study of 181 subjects. *Hum Pathol* 1973; **4**: 319-330
2 **Israel J**. Neue Beobachtungen auf dem Gebiete der Mykosen des Menschen. *Archiv Path Anat Physiol Klin Med* 1978; **74**: 15-53
3 **Kaya E**, Yilmazlar T, Emiroğlu Z, Zorluoğlu A, Bayer A. Colonic actinomycosis: report of a case and review of the literature. *Surg Today* 1995; **25**: 923-926
4 **Coremans G**, Margaritis V, Van Poppel HP, Christiaens MR, Gruwez J, Geboes K, Wyndaele J, Vanbeckevoort D, Janssens J. Actinomycosis, a rare and unsuspected cause of anal fistulous abscess: report of three cases and review of the literature. *Dis Colon Rectum* 2005; **48**: 575-581
5 **de Feiter PW**, Soeters PB. Gastrointestinal actinomycosis: an unusual presentation with obstructive uropathy: report of a case and review of the literature. *Dis Colon Rectum* 2001; **44**: 1521-1525
6 **Uchiyama N**, Ishikawa T, Miyakawa K, Iinuma G, Nakajima H, Ushio K, Yokota T, Akasu T, Shimoda T. Abdominal actinomycosis: barium enema and computed tomography findings. *J Gastroenterol* 1997; **32**: 89-94
7 **Laurent T**, de Grandi P, Schnyder P. Abdominal actinomycosis associated with intrauterine device: CT features. *Eur Radiol* 1996; **6**: 670-673
8 **Polat I**, Gungorduk K, Polat G, Yildirim G, Aslan H, Tekirdag AI. Persistent subumbilical discharge associated with actinomycosis caused by intrauterine contraceptive device: a case report. *Arch Gynecol Obstet* 2008; **277**: 457-460
9 **Mäenpää J**, Taina E, Grönroos M, Söderström KO, Ristimäki T, Närhinen L. Abdominopelvic actinomycosis associated with intrauterine devices. Two case reports. *Arch Gynecol Obstet* 1988; **243**: 237-241
10 **Cintron JR**, Del Pino A, Duarte B, Wood D. Abdominal actinomycosis. *Dis Colon Rectum* 1996; **39**: 105-108
11 **Işik B**, Aydin E, Sogutlu G, Ara C, Yilmaz S, Kirimlioglu V. Abdominal actinomycosis simulating malignancy of the right colon. *Dig Dis Sci* 2005; **50**: 1312-1314
12 **Thanos L**, Mylona S, Kalioras V, Pomoni M, Batakis N. Ileocecal actinomycosis: a case report. *Abdom Imaging* 2004; **29**: 36-38
13 **Valko P**, Busolini E, Donati N, Chimchila Chevili S, Rusca T, Bernasconi E. Severe large bowel obstruction secondary to infection with Actinomyces israelii. *Scand J Infect Dis* 2006; **38**: 231-234
14 **Gidwani AL**, Connolly D, Khan A, Kemohan R, Brown M, Kenny B. Renal, colonic and retroperitoneal actinomycosis--a case report. *West Afr J Med* 2005; **24**: 343-345
15 **Norwood MG**, Bown MJ, Furness PN, Berry DP. Actinomycosis of the sigmoid colon: an unusual cause of large bowel perforation. *ANZ J Surg* 2004; **74**: 816-818
16 **Deshmukh N**, Heaney SJ. Actinomycosis at multiple colonic sites. *Am J Gastroenterol* 1986; **81**: 1212-1214
17 **Meyer P**, Nwariaku O, McClelland RN, Gibbons D, Leach F, Sagalowsky AI, Simmang C, Jeyarajah DR. Rare presentation of actinomycosis as an abdominal mass: report of a case. *Dis Colon Rectum* 2000; **43**: 872-875
18 **Smith TR**. Actinomycosis of the distal colon and rectum. *Gastrointest Radiol* 1992; **17**: 274-276
19 **Kim JC**, Ahn BY, Kim HC, Yu CS, Kang GH, Ha HK, Lee MG. Efficiency of combined colonoscopy and computed tomography for diagnosis of colonic actinomycosis: a retrospective evaluation of eight consecutive patients. *Int J Colorectal Dis* 2000; **15**: 236-242
20 **Umeda T**, Ito K, Kiriyama K, Kondo K, Akiyama S, Takagi H. Pelvic actinomycosis presenting with a rectal stricture: report of a case. *Surg Today* 1994; **24**: 648-650
21 **Coleman RM**, Georg LK, Rozzell AR. Actinomyces naeslundii as an agent of human actinomycosis. *Appl Microbiol* 1969; **18**: 420-426
22 **Berchtenbreiter C**, Brüning R, Auernhammer A, Reiser M. Misleading diagnosis of retroperitoneal actinomycosis. *Eur Radiol* 1999; **9**: 1869-1872
23 **Olson MC**, Demos TC, Tamayo JP. Actinomycosis of the retroperitoneum and an extremity: CT features. *Abdom Imaging* 1993; **18**: 295-297
24 **Ha HK**, Lee HJ, Kim H, Ro HJ, Park YH, Cha SJ, Shinn KS. Abdominal actinomycosis: CT findings in 10 patients. *AJR Am J Roentgenol* 1993; **161**: 791-794
25 **Schmidt P**, Koltai JL, Weltzien A. Actinomycosis of the appendix in childhood. *Pediatr Surg Int* 1999; **15**: 63-65
26 **Skoutelis A**, Petrochilos J, Bassaris H. Successful treatment of thoracic actinomycosis with ceftriaxone. *Clin Infect Dis* 1994; **19**: 161-162
27 **Schlech WF 3rd**, Gelfand M, Alper B, Kaiser AB. Medical management of visceral actinomycosis. *South Med J* 1983; **76**: 921-922
28 **Edelmann M**, Cullmann W, Nowak KH, Kozuschek W. Treatment of abdominothoracic actinomycosis with imipenem. *Eur J Clin Microbiol* 1987; **6**: 194-195

S- Editor Li LF **L- Editor** Cant MR **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.65

World J Gastrointest Surg 2009 November 30; 1(1): 65-67
ISSN 1948-9366 (online)

CASE REPORT

Esophagectomy for a traumatic esophageal perforation with delayed diagnosis

Alexandre Zanchenko Fonseca, Marcelo Augusto Fontenelle Ribeiro Jr, Mariana Frazão, Maurício Campanelli Costas, Lanes Spinelli, Orlando Contrucci

Alexandre Zanchenko Fonseca, Marcelo Augusto Fontenelle Ribeiro Jr, Mariana Frazão, Maurício Campanelli Costas, Lanes Spinelli, Orlando Contrucci, Department of General Surgery, University of Santo Amaro, São Paulo-SP, CEP 04601-060, Brazil

Author contributions: Fonseca AZ, Ribeiro Jr MAF, Frazão M performed the research and wrote the paper; Fonseca AZ, Costas MC, Spinelli L, Contrucci O, Ribeiro Jr MAF operated on the patient.

Correspondence to: Alexandre Zanchenko Fonseca, MD, Department of General Surgery, University of Santo Amaro; Rua Rita Joana de Souza, 42 - Campo Belo, São Paulo-SP, CEP 04601-060, Brazil. azfonseca@hotmail.com

Telephone: +55-11-50446235 Fax: +55-11-32846892
Received: July 2, 2009 Revised: July 16, 2009
Accepted: July 23, 2009
Published online: November 30, 2009

Abstract

Esophageal perforations are rare, and traumatic perforations are even more infrequent. Due to the rarity of this condition and its nonspecific presentation, the diagnosis and treatment of this type of perforation are delayed in more than 50% of patients, which leads to a high mortality rate. An 18-year-old male patient was brought to the emergency room with a penetrating neck injury, caused by a gunshot wound. He was taken to the operating room and underwent surgical exploration of the neck and a chest tube was inserted to treat the hemo- and pneumothorax. During the procedure, a 2 cm lesion was detected in the esophagus, and the patient underwent a primary repair. A contrast leakage into his right hemithorax was noticed on the 4th postoperative day; he was submitted to new surgery, and a subtotal esophagectomy and jejunostomy were performed. He was discharged from the hospital in good condition 20 d after the last procedure. The discussion around this topic focuses on the importance of the timing of diagnosis and the subsequent treatment. In early diagnosed patients, more conservative therapeutics should be performed, such as primary repair, while in those with delayed diagnosis, the patient should be submitted to more aggressive and definitive treatment.

Key words: Delayed perforation treatment; Diagnosis; Esophageal perforation; Esophageal trauma

Peer reviewer: Marc D Basson, MD, PhD, Professor and Chair, Department of Surgery, College of Human Medicine, Michigan State University, 1200 East Michigan Avenue, Suite 655, Lansing, MI 48912, United States

Fonseca AZ, Ribeiro Jr MAF, Frazão M, Costas MC, Spinelli L, Contrucci O. Esophagectomy for a traumatic esophageal perforation with delayed diagnosis. *World J Gastrointest Surg* 2009; 1(1): 65-67 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/65.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.65

INTRODUCTION

Esophageal perforations are rare[1], and traumatic perforations are even more infrequent. In a study by Bladergoreon[2], only 24% of these lesions corresponded to trauma. In 1997, Asensio *et al*[3] published a series of 43 cases in 6 years. Due to the rarity of this condition and its nonspecific presentation, the diagnosis and treatment of these perforations are delayed in more than 50% of patients[2].

This disorder has a high mortality rate, ranging in the literature from 3%-10% if treated within 24 h of the injury and up to 40%-60% if treated after 24 h[2,4]. Recently, these rates have decreased due to improvements in intensive care units, antibiotics and parenteral nutrition[5].

The high mortality rate is directly associated with the delay in diagnosis[6]. This usually occurs because infection spreads to the mediastinum and lungs, leading

to sepsis and multiple organ failure[7].

Several treatment techniques have been reported for this disorder, which indicates that no single surgical procedure could be considered as the gold standard[4]. If the perforation is detected in less than 24 h, the literature supports primary repair and wide drainage of the mediastinum; the treatment for delayed lesions is controversial[4]. Primary repair, single drainage, exclusion procedures, prostheses and resection, with or without primary reconstruction have been described[4].

CASE REPORT

An 18-year-old male patient was brought to the emergency room with a penetrating left side zone I neck injury, caused by a gunshot wound, which had happened 30 min earlier. On physical examination, the bullet exit hole was not identified and auscultation of the breath sounds was diminished in the left hemithorax. At the gunshot entrance site, there was subcutaneous emphysema. He was taken to the operating room and underwent surgical exploration of the neck and a chest tube was inserted to treat the hemo- and pneumothorax. During the procedure, a 2 cm lesion was detected in the esophagus; it was treated with primary repair using a 2 layer interrupted suture. On the 4th postoperative day, an esophagography was performed, where a little contrast leakage into his right hemithorax was noted. As the patient was not recovering as expected, a right thoracotomy was performed. During this surgical procedure, the right lung was incarcerated and a new 4 cm lesion in the esophagus, with necrosis and pus arising from the mediastinum were observed. Due to his bad clinical condition (sepsis and mediastinitis), and despite receiving broad spectrum antibiotics for necrosis of the organ, he underwent a subtotal esophagectomy. A jejunostomy was performed for feeding. The patient was discharged from the hospital 20 d after the last procedure. On his 77th postoperative day, he returned to the service for reconstruction. The surgical approach performed was a gastric tube with a cervical esophagogastric anastomosis with pyloromyotomy. A new esophagography was carried out on the 7th postoperative day, with no signs of leakage. He was discharged on the 14th postoperative day. He has currently been followed up for one year, and is doing well, with good weight gain and normal esophagography (Figure 1).

DISCUSSION

Esophageal perforation is an infrequent condition, with a high mortality rate. The low incidence of this injury leads to inadequate clinical experience in surgeons[4], and for this reason, appropriate management remains controversial[4].

Many authors agree that for those perforations detected early (less than 24 h from injury), the best treatment is primary repair[1,4,6]. For this group of patients, the mortality rates are lower, with less morbidity compared to patients with delayed diagnosis. Port *et al*[6] showed a survival rate of 100%, as did Andrade-Alegre[1]; Normando found a 20% mortality rate. Free perforations can be treated by primary repair; if the perforation is large and repair is not feasible, esophageal resection must be performed.

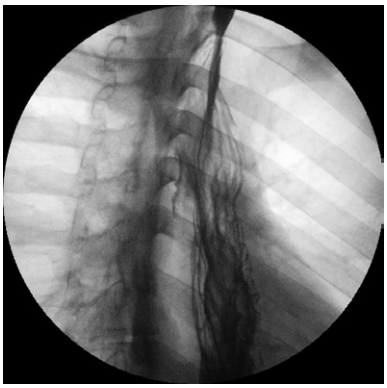


Figure 1 Final aspect of the gastric tube with a cervical esophagogastric anastomosis.

Patients with delayed (more than 24 h) diagnosis represent a serious problem. Generally, they are in a bad clinical condition, needing aggressive and definitive treatment. Most authors think that more aggressive therapy leads to a better outcome. de Andrade *et al*[8] showed a better survival rate in patients who underwent resection rather than primary repair. Salo *et al*[9] found a 68% mortality rate after primary repair in these patients compared with 13% in those who underwent esophagectomy. Similar results were demonstrated by Altorjay *et al*[10] and Orringer *et al*[11]. The literature strongly recommends that esophagectomy should be performed when a clinical condition, such as sepsis and mediastinitis is encountered[6,8].

Data on the non-operative management of this type of perforation have been published. Vogel *et al*[12] support this type of therapy, and showed a survival rate of 100%. They claim that once the perforation and pleural contamination are controlled by adequate drainage, it becomes an esophagocutaneous fistula (*via* chest tube) and will heal similar to most gastrointestinal fistulas. Our group considers that this kind of approach needs to be done with extreme caution and in a selected group of patients, which is small; and as Port *et al*[6] stated, a high level of vigilance should be maintained, to reverse the decision if necessary.

In conclusion, patients with perforations detected early, can be treated more conservatively, with primary repair of the lesion; for those with delayed diagnosis, the literature suggests more aggressive treatment, where esophagectomy is recommended.

REFERENCES

1 **Andrade-Alegre R**. Surgical treatment of traumatic esophageal perforations: analysis of 10 cases. *Clinics* (Sao Paulo) 2005; **60**: 375-380

2 **Bladergroen MR**, Lowe JE, Postlethwait RW. Diagnosis and recommended management of esophageal perforation and rupture. *Ann Thorac Surg* 1986; **42**: 235-239

3 **Asensio JA**, Berne J, Demetriades D, Murray J, Gomez H, Falabella A, Fox A, Velmahos G, Shoemaker W, Berne TV. Penetrating esophageal injuries: time interval of safety for preoperative evaluation--how long is safe? *J Trauma* 1997; **43**: 319-324

4 **Gupta NM**, Kaman L. Personal management of 57 consecutive patients with esophageal perforation. *Am J Surg* 2004; **187**: 58-63

5 **Attar S**, Hankins JR, Suter CM, Coughlin TR, Sequeira A, McLaughlin JS. Esophageal perforation: a therapeutic challenge. *Ann Thorac Surg* 1990; **50**: 45-49; discussion 50-51

6 **Port JL**, Kent MS, Korst RJ, Bacchetta M, Altorki NK. Thoracic esophageal perforations: a decade of experience. *Ann Thorac Surg* 2003; **75**: 1071-1074

7 **Normando R**, Tavares MAF, Azevedo IU, Modesto A, Janahú AJL. Mediastinitis from perforation and rupture of the thoracic esophagus. *Rev Col Bras Cir* 2006; **33**: 361-364

8 **de Andrade AC**, Filho LJFM, Filho MAACL, Alencar AR. Esophagectomy for the esophageal perforation with delayed diagnostic. *Rev Col Bras Cir* 2007 **34**: 432-434

9 **Salo JA**, Isolauri JO, Heikkilä LJ, Markkula HT, Heikkinen LO, Kivilaakso EO, Mattila SP. Management of delayed esophageal perforation with mediastinal sepsis. Esophagectomy or primary repair? *J Thorac Cardiovasc Surg* 1993; **106**: 1088-1091

10 **Altorjay A**, Kiss J, Vörös A, Szirányi E. The role of esophagectomy in the management of esophageal perforations. *Ann Thorac Surg* 1998; **65**: 1433-1436

11 **Orringer MB**, Stirling MC. Esophagectomy for esophageal disruption. *Ann Thorac Surg* 1990; **49**: 35-42; discussion 42-43

12 **Vogel SB**, Rout WR, Martin TD, Abbitt PL. Esophageal perforation in adults: aggressive, conservative treatment lowers morbidity and mortality. *Ann Surg* 2005; **241**: 1016-1021; discussion 1021-1023

S- Editor Li LF **L- Editor** Webster JR **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v1.i1.68

World J Gastrointest Surg 2009 November 30; 1(1): 68-70
ISSN 1948-9366 (online)

CASE REPORT

Enterolithiasis complicating eosinophilic enteritis: A case report and review of literature

Nairuthya Shivathirthan, Gaurav Maheshwari, Dinesh Kamath, Premashish Haldar

Nairuthya Shivathirthan, Gaurav Maheshwari, Dinesh Kamath, Premashish Haldar, Department of Surgical Gastroenterology, Jagjivanram Hospital, Nairuthya S D-78, Jagjivanram Hospital Campus, Maratha Mandir Marg, Mumbai Central, Mumbai 400008, India

Author contributions: Shivathirthan N did the review of literature; Maheshwari G wrote the paper; Haldar P and Kamath D were among the surgery team.

Correspondence to: Dr. Nairuthya Shivathirthan, MS, MRCS, DNB, Department of Surgical Gastroenterology, Jagjivanram Hospital, Nairuthya S D-78, Jagjivanram Hospital Campus, Maratha Mandir Marg, Mumbai Central, Mumbai 400008, India. nairuthya@yahoo.com

Telephone: +91-989-2931360 Fax: +91-161-2495166
Received: April 22, 2008 Revised: June 1, 2008
Accepted: June 8, 2008
Published online: November 30, 2009

Abstract

We report a case of eosinophilic enteritis involving the proximal small bowel, a relatively rare entity, presenting unusually as enteroliths in a 68-year-old man with complaints of anemia, malena and abdominal pain. The disease if diagnosed in the initial stages responds well to medical treatment but if associated with complications or misdiagnosed, surgical modality is the treatment of choice. In our case, the patient presented with enteroliths and strictures. Resection and anastomosis of the small bowel containing stones was carried out. Histopathology confirmed the diagnosis as eosinophilic enteritis.

Key words: Eosinophilic enteritis; Enteroliths; Eosinophils; Gastroenteritis

Peer reviewer: Nikolaus Gassler, Professor, Institute of Pathology, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany

Shivathirthan N, Maheshwari G, Kamath D, Haldar P. Enterolithiasis complicating eosinophilic enteritis: A case report and review of literature. *World J Gastrointest Surg* 2009; 1(1): 68-70 Available from: URL: http://www.wjgnet.com/1948-9366/full/v1/i1/68.htm DOI: http://dx.doi.org/10.4240/wjgs.v1.i1.68

INTRODUCTION

Eosinophilic enteritis, a relatively rare entity, usually involves gastric antrum or proximal small bowel[1]. Eosinophilic gastroenteritis is defined as a disorder that selectively affects the gastrointestinal tract with eosinophil-rich inflammation in the absence of any known causes for eosinophilia[2]. The disease may be asymptomatic or may present as chronic anemia, recurrent abdominal pain, subacute and acute intestinal obstruction or as a rare presentation as enterolithiasis which has not been described previously.

In our case, the patient presented with enteroliths and strictures. Resection and anastomosis of the small bowel containing stones was performed. Histopathology confirmed the diagnosis as eosinophilic enteritis. .

CASE REPORT

A 68-year-old man was referred to us with complaints of chronic anemia, malena and abdominal pain for 15 years. The patient had been evaluated earlier and had been transfused on multiple occasions. His past medical profile was not suggestive of any associated medical condition and there was no history of use of herbal medications or excessive intake of tea or coffee. Baseline blood investigations, chest X-ray and ECG were normal. Stool for occult blood was positive. Upper gastrointestinal endoscopy and colonoscopy were normal. Ultrasound of the abdomen did not reveal any evidence of cholecystitis or cholelithiasis. The patient underwent a small bowel enteroclysis which revealed multiple strictures in the distal

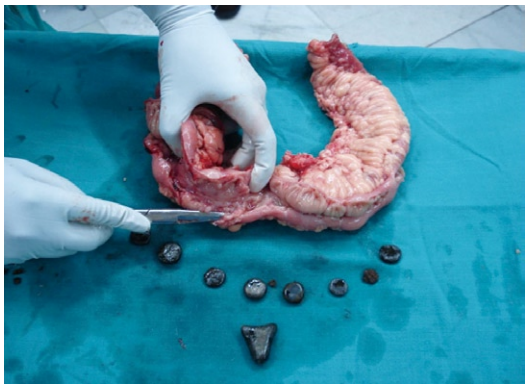


Figure 1 Intraoperative photography showing resected small bowel segment with enteroliths.

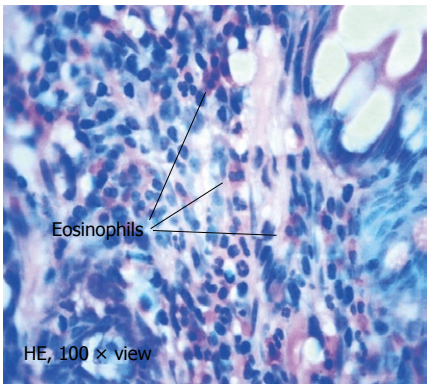


Figure 2 Histophotomicrography of specimen showing transmural eosinophilic infiltrate (HE, × 100).

jejunum and proximal ileum with filling defects suggestive of enteroliths. The patient was subjected to exploratory laparotomy through a midline incision. There were multiple strictures at the junction of distal jejunum and proximal ileum with sacculations in between containing more than 10 enteroliths measuring between 4-20 mm (Figure 1). Resection and anastomosis of the small bowel containing stones was then carried out. The resected specimen was sent for histopathological examination. Abdomen was drained and closed in layers. The pathological report of the small bowel containing the enteroliths showed dense transmural infiltration of eosinophils, and eosinophilic enteritis was diagnosed (Figure 2). The biochemical analysis of the stones retrieved from the bowel showed the presence of calcium and oxalate crystals along with concretions of ingested vegetable fibre. Calcium oxalate was reported to be the major component of these stones. The patient had uneventful recovery and was discharged on the 10th postoperative day.

DISCUSSION

Primary eosinophilic gastrointestinal disorders are defined as disorders that selectively affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes for eosinophilia (e.g. drug reactions, parasitic infections, and malignancy)[2]. These disorders include eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis and are occurring with increasing frequency[3]. The symptoms depend on the site of infiltration and the layers affected. High blood levels of eosinophils are usually present. Computed tomography plays a fundamental role in the evaluation of this disease[4].

In contrast to the esophagus, the stomach and intestine have readily detectable baseline eosinophils under healthy conditions. Eosinophilic gastritis, enteritis and gastroenteritis are grouped together because they are clinically similar and there is a paucity of information available concerning their pathogenesis. However, it is likely that they are indeed distinct entities in most patients. These diseases are characterized by the selective infiltration of eosinophils in the stomach, small intestine, or both, with variable involvement of the esophagus, large intestine, or both[5,6]. It is now appreciated that many disorders are accompanied by eosinophil infiltration in the stomach, such as parasitic and bacterial infections (including *Helicobacter pylori*), IBD, hypereosinophilic syndrome (HES), eosinophilic enteritis, periarteritis, allergic vasculitis, scleroderma, drug injury, and drug hypersensitivity[7]. These disorders are classified into primary and secondary subtypes. The primary subtype includes the atopic, nonatopic, and familial variants, whereas the secondary subtype is divided into two groups, one is composed of systemic eosinophilic disorders (HES) and the other is composed of non eosinophilic disorders. Primary eosinophilic enteritis, gastritis and gastroenteritis have also been called idiopathic or allergic gastroenteropathy. The familial form has not been well characterized. Primary eosinophilic gastroenteritis encompasses multiple disease entities subcategorized into three types on the basis of the histologic involvement: mucosal, muscularis and serosal forms[8]. Of note, either layer of the gastrointestinal tract can be involved, so that endoscopic biopsy can be normal in patients with the muscularis subtype, serosal subtype, or both. No standards are available for the diagnosis of eosinophilic gastritis or gastroenteritis, but a few findings support the diagnosis[9]. For example, the presence of increased eosinophils in biopsy specimens from the gastrointestinal tract wall, the infiltration of eosinophils within intestinal crypts and gastric glands, the lack of involvement of other organs, and the exclusion of other causes of eosinophilia (e.g. infections and IBD) are supportive of eosinophilic gastroenteritis. The clinical presentations of eosinophilic enteritis depend on the site of involvement with eosinophilic enterits being asymptomatic or symptomatic. Symptomatic cases may present as chronic anemia, subacute intestinal obstruction due to strictures, acute obstruction due to intussusceptions or chronic abdominal pain[1,2,6].

Enteroliths, the endogenous foreign bodies, were first described by Pfahler and Stamm in 1915. True enteroliths of the small intestine are of three main types: (1) those consisting mainly of bile acids; (2) those consisting mainly of calcium oxalate; and (3) those consisting mainly of phosphate. Bile acid enteroliths are made up mainly of choleic acid.

The maximum size reported in the literature is more than 6 cm, and maximum number is up to 1400 enteroliths proximal to a postoperative stricture in a patient who had surgery for colon carcinoma[10]. Most of the conditions causing enteroliths are due to stasis or hypermotility[10]. Enteroliths in association with eosinophilic enteritis has not been reported so far in the literature to the best of our knowledge. Judging from published reports, cases of stones in the small intestine are rare. In the literature, the composition is described only in general terms. It would no doubt increase our understanding of the subject, and probably of lithiasis in general, if all such stones were reported and analysed as completely as possible.

REFERENCES

1 **Kshirsagar AY**, Jagtap SV, Kanojiya RP, Langade YB, Shinde SL, Shekhar N. Eosinophilic enteritis presenting as a rare cause for ileo-ileal intussusception. *World J Gastroenterol* 2007; **13**: 6444-6445

2 **Shin WG**, Park CH, Lee YS, Kim KO, Yoo KS, Kim JH, Park CK. Eosinophilic enteritis presenting as intussusception in adult. Korean *J Intern Med* 2007; **22**: 13-17

3 **Rothenberg ME**. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004; **113**: 11-28; quiz 29

4 **Ahualli J**, Méndez-Uriburu L, Ravera ML, Raimondo MA, Ortiz Mayor M. [Primary eosinophilic enteritis: a case report] *Radiologia* 2007; **49**: 272-274

5 **Torpier G**, Colombel JF, Mathieu-Chandelier C, Capron M, Dessaint JP, Cortot A, Paris JC, Capron A. Eosinophilic gastroenteritis: ultrastructural evidence for a selective release of eosinophil major basic protein. *Clin Exp Immunol* 1988; **74**: 404-408

6 **Katz AJ**, Twarog FJ, Zeiger RS, Falchuk ZM. Milk-sensitive and eosinophilic gastroenteropathy: similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984; **74**: 72-78

7 **Ahmad M**, Soetikno RM, Ahmed A. The differential diagnosis of eosinophilic esophagitis. *J Clin Gastroenterol* 2000; **30**: 242-244

8 **Klein NC**, Hargrove RL, Sleisenger MH, Jeffries GH. Eosinophilic gastroenteritis. *Medicine* (Baltimore) 1970; **49**: 299-319

9 **Kelly KJ**. Eosinophilic gastroenteritis. *J Pediatr Gastroenterol Nutr* 2000; **30** Suppl: S28-S35

10 **Klingler PJ**, Seelig MH, Floch NR, Branton SA, Metzger PP. Small-intestinal enteroliths--unusual cause of small-intestinal obstruction: report of three cases. *Dis Colon Rectum* 1999; **42**: 676-679

S- Editor Zhong XY **L- Editor** Ma JY **E- Editor** Lin YP

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
www.wjgnet.com

World J Gastrointest Surg 2009 November 30; 1(1): I
ISSN 1948-9366 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Surgery*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Surgery*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Giuseppe Aprile, MD, Department Of Medical Oncology, University Hospital of Udine, Piazzale S Maria della Misericordia, 33100 Udine, Italy

Eelco de Bree, MD, PhD, Assistant Professor of Surgery, Department of Surgical Oncology, University Hospital, PO Box 1352, 71110 Herakleion, Greece

Julio Coelho, MD, PhD, Professor of Surgery and Chief, Division of Gastrointestinal Surgery and Liver Transplantation, Federal University of Parana, Brazil

Marc D Dahlke, MD, PhD, Department of Surgery, University of Regensburg Medical Center, Franz Josef Strauss Allee 12, 93042 Regensburg, Germany

Reinhart T Grundmann, Professor, Wissenschaftlich medizinischer Direktor, Kreiskliniken Altötting-Burghausen, Krankenhausstr. 1, D- 84489 Burghausen, Germany

Mary Margaret Kemeny, MD, FACS, Director, Queens Cancer Center, Queens Hospital Center/Mt. Sinai Services, Professor of Surgery, Mt Sinai School of Medicine, 82-68 164th St, Queens, NY 11432 United States

Gozde KIR, Associate Professor of Pathology, Chief of the Pathology Department, Umraniye Education and Research Hospital, 34760 Umraniye-Istanbul, Turkey

Tsuyoshi Konishi, MD, PhD, Department of Gastroenterological Surgery, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo, 135-8550, Japan

Guido AM Tiberio, Professor, Surgical Clinic, Department of Medical and Surgical Sciences, University of Brescia, Viale Europa 17, 25100 Brescia, Italy

Marcus Vinicius Motta Valadão, MD, Rua Paissandu 385/302, flamengo, Rio de Janeiro-RJ, CEP: 22210-080, Brazil

WJGS

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
www.wjgnet.com

World J Gastrointest Surg 2009 November 30; 1(1): I
ISSN 1948-9366 (online)

Meetings

Events Calendar 2009-2010

December 3-4, 2009
Pancreatic Society of Great Britain & Ireland Annual Scientific Meeting
Weetwood Hall, Otley Road, Leeds, LS16 5PS, United Kingdom

January 15-16, 2010
AGA Clinical Congress of Gastroenterology and Hepatology
The Venetian And Palazzo, 3355 Las Vegas Blvd South,
Las Vegas, United States
http://www.gilearn.org/clinical-congress

January 27-31, 2010
Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
http://www.alpshpbmeeting.soton.ac.uk

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, W1G 0AE, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 4-7, 2010
2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue
St. Louis, Missouri 63101 United States
http://www.surgonc.org/

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver (APASL)
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

April 14-18, 2010
The International Liver Congress™ 2010
European Association for the Study of the Liver
Vienna, Austria

May 1-5, 2010
2010 American Transplant Congress
San Diego Convention Center, 111 West Harbor Drive
San Diego, CA 92101, United States
http://www.atcmeeting.org/2010

May 1-5, 2010
Digestive Disease Week 2010
American Association for the Study of Liver Diseases
Ernest N. Morial Convention Center, 900 Convention Center Blvd, New Orleans, LA 70130, United States
http://www.ddw.org/

May 15-19, 2010
Annual Meeting of the American Society of Colon and Rectal Surgeons
Hilton Minneapolis Hotel & Convention Center, Minneapolis,
Minnesota, United States
http://www.fascrs.org/

September 16-18, 2010
Prague Hepatology Meeting 2010
Prague, Czech Republic
http://www.congressprague.cz/en/kongresy/phm2010.html

October 20-23, 2010
Australian Gastroenterology Week
Melbourne, Australia
http://www.gesa.org.au/agw.cfm

WJGS World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
www.wjgnet.com

World J Gastrointest Surg 2009 November 30; 1(1): I -IV
ISSN 1948-9366 (online)

Instructions to authors

GENERAL INFORMATION

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 328 experts in gastrointestinal surgery from 35 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGS* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGS* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGS* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

The major task of *WJGS* is to report rapidly the most recent advances in basic and clinical research on gastrointestinal oncology. The topics of *WJGS* cover the carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. This cover epidemiology, etiology, immunology, molecular oncology, cytology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, nutrition, diagnosis and therapeutics. This journal will also provide extensive and timely review articles on oncology.

The columns in the issues of *WJGS* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (8) Original Article: To originally report the innovative and valuable findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal surgery; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGS*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal surgery; (13) Guidelines: To introduce Consensuses and Guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal surgery.

CSSN
ISSN 1948-9366 (online)

Published by
Beijing Baishideng BioMed Scientific Co., Ltd.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Beijing Baishideng BioMed Scientific Co., Ltd, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory

animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the International Committee of Medical Journal Editors to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www. clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/1948-9366office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-9366/index.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjgs@wjgnet.com, or by telephone: +86-10-85381891. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g., Telephone: +86-10-59080039, Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJGS*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words). Available from:http://www.wjgnet.com/wjg/help/8.doc

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/wjg/help/instructions.jsp.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are

applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer

disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*

Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*

Biology: *H. pylori*, *E coli*, *etc.*

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJGS*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Gastrointestinal Surgery
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjgs@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381891
Fax: +86-10-85381893

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1007-9327/news/10.doc.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1007-9327/news/12.doc.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJGS will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

Authors of accepted articles must pay a publication fee.
EDITORIAL, TOPIC HIGHLIGHTS, BOOK REVIEWS and LETTERS TO THE EDITOR are published free of charge.