World Journal of *Surgical Procedures*

World J Surg Proced 2013 November 28; 3(3): 18-59



World Journal of Surgical Procedures

A peer-reviewed, online, open-access journal of surgical procedures

Editorial Board

2011-2015

The World Journal of Surgical Procedures Editorial Board consists of 276 members, representing a team of worldwide experts in surgical procedures. They are from 35 countries, including Australia (10), Austria (3), Belgium (1), Brazil (4), Canada (5), China (23), Egypt (2), France (1), Germany (10), Greece (9), Hungary (1), India (6), Iran (3), Ireland (1), Israel (6), Italy (29), Japan (34), Lebanon (1), Lithuania (1), Mexico (2), Netherlands (2), Nigeria (1), Norway (1), Pakistan (1), Poland (1), Romania (2), Saudi Arabia (1), Singapore (2), South Korea (7), Spain (11), Switzerland (5), Thailand (1), Turkey (7), United Kingdom (11), and United States (71).

PRESIDENT AND EDITOR-IN-CHIEF

Massimo Chello, Rome Feng Wu, Oxford

GUEST EDITORIAL BOARD MEMBERS

Da-Tian Bau, *Taichung* Chiung-Nien Chen, *Taipei* Chong-Chi Chiu, *Tainan* Shah-Hwa Chou, *Kaohsiung* Po-Jen Ko, *Taoyuan* Jen-Kou Lin, *Taipei* Shu-Min Lin, *Taoyuan* Chin-su Liu, *Taipei* Shi-Ping Luh, *Taipei* Sheng-Lei Yan, *Changhua*

MEMBERS OF THE EDITORIAL BOARD



Saleh Mahdi Abbas, Victoria Savio George Barreto, Adelaide Adam Bryant, Melbourne Terence C Chua, Sydney C Augusto Gonzalvo, Victoria Glyn Garfield Jamieson, Adelaide Neil Merrett, Sydeny David Lawson Morris, Sydney Carlo Pulitanò, Sydney Zhong-hua Sun, Perth

Austria

Ojan Assadian, Vienna Herwig R Cerwenka, Graz

Rupert Menapace, Vienna



Yi-cheng Ni, Leuven



Cesar Augusto Galvao Arrais, *São Paulo* Jo ao LM Coutinho de Azevedo, *São Paulo* Djalma José Fagundes, *São Paulo* Hermes Pretel, *São Paulo*



Walid M El Moghazy Shehata, Edmonton Line Jacques, Montreal Tatsuya Kin, Edmonton Michele Molinari, Halifax Wiseman Sam, Vancouver



Yong An, Chongqing Andrew Burd, Hong Kong De-Liang Fu, Shanghai Di Ge, Shanghai Lan Huang, Chongqing Xiao-Long Li, Tianjin Yan Li, Wuhan Simon Siu-Man Ng, Hong Kong Qiang Wang, Shanghai Yong-Ming Yao, Beijing Anthony Ping-Chuen Yim, Hong Kong Dan Zhu, Wuhan Jiang-Fan Zhu, Shanghai



Samer Saad Bessa, *Alexandria* Ahmed El SaID Ahmed Lasheen, *Zagazig*



Michel Henry, Nancy



Hans G Beger, Ulm Uta Dahmen, Jena Alexander E Handschin, Braunschweig Tobias Keck, Nürnberg Uwe Klinge, Aachen Philipp Kobbe, Aachen Matthias W Laschke, Homburg M Javad Mirzayan, Hannover Robert Rosenberg, München Wolfgang Vanscheidt, Breisgau



Giannoukas D Athanasios, Larissa Eelco de Bree, Heraklion Fotis E Kalfarentzos, Patras Dimitris Karnabatidis, Patras Peppa Melpomeni, Athens Kosmas I Paraskevas, Athens Aristeidis Stavroulopoulos, Athens Demosthenes Ziogas, Ioannina Odysseas Zoras, Heraklion





Péter Örs Horváth, Pécs



Nilakantan Ananthakrishnan, Pondicherry Rakesh Kumar, Haryana Suguna Lonchin, Chennai Chinmay Kumar Panda, Kolkata Muthukumaran Rangarajan, Coimbatore Nihal Thomas, Vellore



Mehrdad Mohammadpour, *Tehran* Seyed Reza Mousavi, *Tehran* Mohammad Taher Rajabi, *Tehran*



Desmond Winter, Dublin



Nimer Najib Assy, Safed Haim Gutman, Tikva Yoav Mintz, Jerusalem Solly Mizrahi, Beer sheva Nir Wasserberg, Petach Tiqua Oded Zmora, Tel Hashomer



Ferdinando Agresta, Fregona Franco Bassetto, Padova Claudio Bassi, Verona Gabrio Bassotti, Perugia Francesco Boccardo, Genoa Giuseppe Brisinda, Rome Fausto Catena, Bologna Luigi D'Ambra, La Spezia Alessandro Franchini, Florence Giuseppe Galloro, Naples Massimo Gerosa, Verona Francesco Greco, Brescia Roberto Iezzi, Rome Fabrizio Luca Milan Simone Mocellin, Padova Boscolo-Rizzo Paolo, Padua Giacomo Pata, Brescia Marcello Picchio, Latina Giuseppe Piccinni, Bari Marco Raffaelli, Rome Matteo Ravaioli, Bologna Raffaele Russo, Naples Vincenzo Russo, Naples Pierpaolo Sileri, Rome Luciano Solaini, Ravenna Pietro Valdastri, Pisa Luca Viganò, Torino Luigi Zorcolo, Cagliari



Hiroki Akamatsu, Osaka Mitsuhiro Asakuma, Osaka Hideo Baba, *Kumamoto* Akihiro Cho, Chiba Shotaro Enomoto, Wakayama Satoshi Hagiwara, Yufu Yoshiki Hirooka, Nagoya City Motohiro Imano, Osaka Yasuhiro Ito, Kobe Koichi Iwatsuki, Osaka Kyousuke Kamada, Asahikawa Hirotoshi Kobayashi, Tokyo Makoto Kume, Gifu Daisuke Morioka, Yokohama Toshitaka Nagao, Tokyo Nobuhiro Ohkohchi, Tsukuba Kensaku Sanefuji, Fukuoka Norio Shiraishi, Oita Yasuhiko Sugawara, Tokyo Nobumi Tagaya, Koshigaya Sonshin Takao, Kagoshima Hiroshi Takeyama, Tokyo Koji Tanaka, Suita Kuniya Tanaka, Yokohama Shinji Tanaka, Tokyo Akira Tsunoda, Kamogawa Dai Uematsu, Nagano Shinichi Ueno, Kagoshima Toshifumi Wakai, Niigata Atsushi Watanabe, Sapporo Toshiaki Watanabe, Tokyo Yo-ichi Yamashita, Hiroshima Naohisa Yoshida, Kyoto Seiichi Yoshida, Niigata



Bishara Atiyeh, Beirut



Aleksandras Antusevas, Kaunas



Mexico

José A Robles Cervantes, Guadalajara Miguel F Herrera, Mexico City



Netherlands

Frans L Moll, *Utrecht* Paulus Joannes van Diest, *Utrecht*



Christopher Olusanjo Bode, Lagos

Norway



Michael Brauckhoff, Bergen







Ali Doğan Bozdağ, Aydin Mehmet Fatih Can, Ankara Süleyman Kaplan, Samsun Cuneyt Narin, Konya Cem Kaan Parsak, Adana Taner Tanriverdi, Istanbul



Basil Jaser Ammori, Manchester Sanjoy Basu, Ashford Justin Davies, Cambridge Gianpiero Gravante, Leicester Sanjeev Kanoria, London James Kirkby-Bott, London Anastasios Koulaouzidis, Edinburgh Kefah Mokbel, London Mikael Hans Sodergren, London Emmanouil Zacharakis, London

United States

Amir Abolhoda, Orange Mohammad Al-Haddad, Indianapolis Mario Ammirati, Columbus Gintaras Antanavicius, Warminster Mustafa K Başkaya, Madison Ronald Scott Chamberlain, Livingston Steven D Chang, Stanford Yi-Jen Chen, Duarte Gregory S Cherr, Buffalo Gilwoo Choi, Redwood Danny Chu, Houston Gaetano Ciancio, Florida John V Conte, Maryland Daniel R Cottam, Henderson Ruy J Cruz Jr, Pittsburgh Steven C Cunningham, Baltimore Juan C Duchesne, New Orleans Andrew J Duffy, New Haven Konstantinos P Economopoulos, Boston Sukru H Emre, New Haven Thomas Joseph Fahey, New York John F Gibbs, Buffalo Eric Joseph Grossman, Chicago Andrew A Gumbs, Berkeley Heights Walter Hall, *Syracuse* Jeffrey Burke Halldorson, Washington Michael R Hamblin, Boston Hobart W Harris, Francisco Steven N Hochwald, Gainesville John A Hovanesian, Laguna Hills Sergio Huerta, Dallas Alexander Iribarne, New York David M Kahn, Pala Alto Kanav Kahol, Arizona Lewis J Kaplan, New Haven Randeep Singh Kashyap, New York Chung H Kau, Birmingham Melina Rae Kibbe, Chicago Rong-pei Lan, San Antonio

I Michael Leitman, New York Julian Emil Losanoff, Las Vegas Amosy Ephreim M'Koma, Nashville Joseph Keith Melancon, Washington Kresimira M Milas, Cleveland Mark Daniel Morasch, Billings Majid Moshirfar, Salt Lake City Kamal Nagpal, Riveredge Scott R Owens, Ann Arbor Timothy Michael Pawlik, Baltimore Raymond M Planinsic, Pittsburgh Guillermo Portillo-Ramila, San Antonio TS Ravikumar, Danville Jonathan C Samuel, Chapel Hill Mark J Seamon, Camden Jatin P Shah, New York Herrick J Siegel, Birmingham Brad Elliot Snyder, Houston Allan S Stewart, New York Rakesh M Suri, Rochester Bill Tawil, Los Angeles Swee Hoe Teh, San Francisco James Fallon Thornton, Dallas R Shane Tubbs, Birmingham Andreas Gerasimos Tzakis, Pittsburgh Jiping Wang, Boston Hongzhi Xu, Boston Hua Yang, Ann Arbor Rasa Zarnegar, San Francisco Zhong Zhi, Charleston Wei Zhou, Stanford Robert Zivadinov, Buffalo



World Journal of Surgical Procedures

Contents		Four-monthly Volume 3 Number 3 November 28, 2013
REVIEW	18	Intraperitoneal drains during open appendicectomy for gangrenous and perforated appendicitis <i>Gravante G, Overton J, Elshaer M, Sorge R, Kelkar A</i>
MINIREVIEWS	25	Retroileal trans-mesenteric colorectal anastomosis Sileri P, Capuano I, Ciangola CI, Franceschilli L, Giorgi F, Gaspari AL
	29	Platelet therapy: A novel strategy for liver regeneration, anti-fibrosis, and anti-apoptosis Takahashi K, Murata S, Ohkohchi N
BRIEF ARTICLE	37	Treatment of cervico-mediastinal goiters Magistrelli P, D'Ambra L, Bonfante P, Francone E, Leoncini R, Cappagli M, Falco E
	41	Operative indications of follicular type tumors, based on Japanese clinical guidelines Takeyama H, Tabei I, Kato K, Kamio M, Nogi H, Toriumi Y, Kinoshita S, Akiba T, Uchida K, Morikawa T
META-ANALYSIS	47	Back to basics: A meta-analysis of stump management during open appendicectomy for uncomplicated acute appendicitis <i>Gravante G, Yahia S, Sorge R, Mathew G, Kelkar A</i>
CASE REPORT	54	Epidermoid cyst of intrapancreatic accessory spleen: A case report and literature review Lee CL, Di Y, Jiang YJ, Jin C, Fu DL



Contents		J Volume	<i>World Journal of Surgical Procedures</i> 3 Number 3 November 28, 2013		
APPENDIX I-1	V	Instructions to authors			
ABOUT COVER		Editorial Board Member of <i>World Journa</i> Gianpiero Gravante, BSC, MBBS, PhD, tering General Hospital, Rothwell Road	al of Surgical Procedures, Department of Colorectal Surgery, Ket- 10, NN16 8UZ Kettering, United Kindom		
AIM AND SCOPE		World Journal of Surgical Procedures (World J. DOI: 10.5412) is a peer-reviewed open at clinical practice and improve diagnostic and <i>WJSP</i> covers topics concerning ambu surgical procedures, digestive system surgical obstetric surgical procedures, neurosurg procedures, oral surgical procedures, orth surgical procedures, reconstructive surgica urogenital surgical procedures, computer-as procedures, and minimally invasive, surgica techniques, anastomosis, assisted circulation, non-therapeutic, curettage, debridement, de- removal, dissection, drainage, electrosurge intraoperative care, laparotomy, ligation, lymp monitoring, intraoperative, ostomy, paracen postoperative care, preoperative care, prosth surgery, splenectomy, suture techniques, sy transplantation, diagnostic imaging, and end We encourage authors to submit their to manuscripts that are supported by major	Surg Proced, WJSP, online ISSN 2219-2832, ccess academic journal that aims to guide therapeutic skills of clinicians. latory surgical procedures, cardiovascular l procedures, endocrine surgical procedures, ical procedures, ophthalmologic surgical nopedic procedures, otorhinolaryngologic l procedures, thoracic surgical procedures, ssisted surgical procedures, elective surgical l procedures, specifically including ablation , bariatric surgery, biopsy, body modification, compression, deep brain stimulation, device ery, extracorporeal circulation, hemostasis, ph node excision, mastectomy, microsurgery, tesis, pelvic exenteration, perioperative care, nesis implantation, reoperation, second-look mphysiotomy, tissue and organ harvesting, oscopy. manuscripts to <i>WJSP</i> . We will give priority enational and international foundations and ificance.		
INDEXING/ABSTRACTING		World Journal of Surgical Procedures is now inde	xed in Digital Object Identifier.		
FLYLEAF I-1	III	Editorial Board			
EDITORS FOR Responsible Assistant Editor: Xin-Xin Che Responsible Science Editor: Xin-Xia Song THIS ISSUE Proofing Editor-in-Chief: Lian-Sheng Ma Proofing Editor-in-Chief: Lian-Sheng Ma					
NAME OF JOURNAL World Journal of Surgical Procedures ISSN ISSN 2219-2832 (online) LAUNCH DATE December 29, 2011 FREQUENCY Four-monthly EDITORS-IN-CHIEF Massimo Chello, MD, Professor, Department of a diovascular Sciences, University Campus Bio Medice Rome, Via Alvaro Del Portillo 200, 00128 Rome, Italy Feng Wu, MD, PhD, Professor, Nuffield Dep ment of Surgical Sciences, University of Oxford, L 6, John Radcliffe Hospital, Headley Way, Oxford, C 9DU, United Kingdom EDITORIAL OFFICE	Car- o of ly part- evel OX3	Xiu-Xia Song, Vice Director World Journal of Surgical Procedures Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China Telephone: +86-10-85381891 Fax: +86-10-85381893 E-mail: bgooffice@wignet.com http://www.wignet.com PUBLISHER Baishideng Publishing Group Co., Limited Flat C, 23/F, Lucky Plaza, 315-321 Lockhart Road, Wan Chai, Hong Kong, China Fax: +852-65557188 Telephone: +852-31779906 E-mail: bggoffice@wignet.com http://www.wignet.com PUBLICATION DATE	COPYRIGHT © 2013 Baishideng Publishing Group Co., Limited. Articles published by this Open Access journal are dis- tributed under the terms of the Creative Commons At- tribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non com- mercial and is otherwise in compliance with the license. SPECIAL STATEMENT All articles published in this journal represent the viewpoints of the authors except where indicated oth- erwise. INSTRUCTIONS TO AUTHORS Full instructions are available online at http://www.wjg- net.com/2219-2832/g_info_20100722180909.htm. ONLINE SUBMISSION		
Jin-Lei Wang, Director		November 28, 2013	http://www.wjgnet.com/esps/		



World Journal of **Surgical Procedures**

Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.5412/wjsp.v3.i3.18 World J Surg Proced 2013 November 28; 3(3): 18-24 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

REVIEW

Intraperitoneal drains during open appendicectomy for gangrenous and perforated appendicitis

Gianpiero Gravante, John Overton, Mohamed Elshaer, Roberto Sorge, Ashish Kelkar

Gianpiero Gravante, Mohamed Elshaer, Ashish Kelkar, Department of Colorectal Surgery, Kettering General Hospital, Kettering, Northamptonshire, NN16 8UZ, United Kingdom John Overton, Department of Colorectal Surgery, Royal Oldham Hospital, Oldham, OL1 2JH, United Kingdom Roberto Sorge, Department of Human Physiology, Laboratory of Biometry, University of Tor Vergata, 00133 Rome, Italy Author contributions: Gravante G and Kelkar A ideated the study; Gravante G, Overton J, Elshaer M and Sorge R collected the articles, analysed their results and wrote the review; all authors critically revised the study and approved the final draft. Correspondence to: Gianpiero Gravante, BSC, MBBS, PhD, Department of Colorectal Surgery, Kettering General Hospital, Rothwell Road 10, Kettering, Northamptonshire, NN16 8UZ, United Kingdom. ggravante@hotmail.com Telephone: +44-11-62168244 Fax: +39-62-33216592 Received: September 8, 2013 Revised: November 6, 2013

Accepted: November 20, 2013

Published online: November 28, 2013

Abstract

Intra-abdominal drains are still routinely used in the surgical management of gangrenous and perforated appendicitis. A systematic review was performed with the aim of establishing their influence on postoperative complications in such cases. A literature search was conducted using the search engines PubMed and Cochrance Central Register of Controlled Trials. Included were retrospective case-controlled and prospective randomized controlled trials on the use of drain for open appendicectomy in gangrenous and perforated appendicitis. Twelve articles were found that met the inclusion criteria. Intrabdominal abscesses, postoperative ileus, surgical site infections, fecal fistulas and burst abdomen had significant higher incidences in the drain vs non drain group (10.3%, 20.3%, 32.5%, 3.4% and 5.7% vs 4.7%, 8.5%, 16.2%, 0% and 0%, respectively). In most cases the risk was more than doubled in the drain group compared to the non-drain one. There were no significant differences among groups in terms

of mortality while the results were underpowered to effectively evaluate wound dehiscence and adhesions. The use of intra-abdominal drains in the management of gangrenous and perforated appendicitis by open appendicectomy is associated with an increased rate of common postoperative complications.

 \odot 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Appendix; Appendicectomy; Complications; Infections; Drains

Core tip: The prophylactic use of intraperitoneal drains for the prevention of postoperativeabdominal abscesses in cases of gangrenous or perforated appendicitis remains a contentious issue, particularly considering that recent enhanced recovery programs have frequently excluded their usage in colorectal operations. With regards to open appendicectomy, most studies demonstrate an increase in the incidence of postoperative abscesses, ileus and surgical site infections in patients in whom a drain was used and currently question their routine in cases of gangrenous and perforated appendicitis.

Gravante G, Overton J, Elshaer M, Sorge R, Kelkar A. Intraperitoneal drains during open appendicectomy for gangrenous and perforated appendicitis. *World J Surg Proced* 2013; 3(3): 18-24 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/18.htm DOI: http://dx.doi. org/10.5412/wjsp.v3.i3.18

INTRODUCTION

The use of intraperitoneal drains in abdominal surgery is a long-standing and still highly controversial practice^[1]. It was thought that they removed contaminated material



from the abdominal cavity and reduced the risk of forming intra-abdominal abscesses (IAAs)^[2,3]. Indications for the insertion of drains were mostly based on personal experiences and preferences rather than on scientific grounds ("When in doubt, drain" - Tait 1905, cited by Yates^[2] and Johnson et al^[3]). Numerous trials and metaanalysis have challenged their routine use, for example in colorectal surgery where they do not decrease mortality, anastomotic dehiscences, surgical site infections (SSIs), re-interventions or extra-abdominal complications^[4-6], Conversely, intra-abdominal drains have been shown to contribute to postoperative ileus and increase the length of stay. Based on these findings intraperitoneal drains have been abandoned by most enhanced recovery programs for elective colorectal surgery^[6-8] and their role has been limited to therapeutic purposes in cases of postoperative pelvic collections.

The use of intra-abdominal drains as part of the management of gangrenous and perforated appendicitis by open appendicectomy remains an unresolved issue^[9]. The indications for the use of drains in this context are not clear and the clinical practice is operator-dependent and not evidence based. Some advocate Penrose drains in which the internal lumen allows the fluid to drain by capillary action (open drain), as opposed to single lumen silicone drains connected to a suction chamber (Hemovac or Redivac) or double lumen drains connected to suction device (Jackson-Pratt drains), both closed suction devices.

The aim of this systematic review was to establish through an analysis of the reported rates of postoperative complications whether or not there is an indication for the use of intra-abdominal drains during the open surgical management of gangrenous and perforated appendicitis.

SEARCH STRATEGY, OUTCOMES AND STATISTICS

Articles were systematically reviewed from the results of the following searches conducted using the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) search engines: "appendicitis AND drain" (n = 664), "open AND appendicectomy AND drain" (n = 63), "appendicectomy AND drain" (n = 140). Included were retrospective case-controlled studies and prospective randomized controlled trials reporting the postoperative complication rates for patients with gangrenous and perforated appendicitis managed by open appendicectomy who either did or did not receive an intra-abdominal drain during surgery. An acute appendicitis with an already concomitant periappendicitis abscess was considered in the group of perforated appendicitis. Excluded were all studies including cases of endoappendicitis, phlegmonous or catarrhal appendicitis, those that did not report a comparison between the use of drain vs non drain, case reports, studies on laparoscopic appendirectomy or those comparing open vs laparoscopic appendicectomy, reviews, those regarding the management of appendicular mass, those in which drains were used to treat an abscess *via* a percutaneous drainage, cost analysis studies.

Primary end-point of the study was to examine the influence of intraperitoneal drains in preventing postoperative IAAs following open appendicectomy for gangrenous and perforated appendicitis. Secondary endpoints were the relationships between drains and the occurrence of other postoperative complications such as SSIs, wound dehiscence, adhesions, fecal fistula, burst abdomen and mortality. All studies reporting data on IAAs only, secondary outcomes only, or both were included in the review and data were analysed in the specific chapters. A specifically designed data form was generated in order to capture the demographics and reported rates of postoperative complications considered. Data analysis was performed by two researchers (Gravante G and Sorge R).

Statistical analysis

All data were inserted into an Excel database (Microsoft, Redmond, Washington - United States). Parameters evaluated were categorized either as "present" or "absent" (categorical variables) and descriptive statistics used were frequencies. Analysis of comparison between groups was conducted with the χ^2 test or Fisher's exact test if counts were less than five. The power calculation was verified for each complication and reported. The odds ratio for the use of drains on the occurrence of postoperative complications was also calculated. *P* values less than 0.05 were considered statistically significant.

LITERATURE AVAILABLE

A total of 871 articles were identified, which were assessed by 2 authors (Gravante G and Overton J) using the PRISMA flow diagram for systematic reviews (Figure 1)^[10]. Following the removal of duplicated articles the number of articles screened was 719. Two hundred and forty seven articles were directly excluded from the analysis because their title and abstract made it immediately apparent that they were not relevant to the study question. The titles and abstract of the remaining 472 articles were assessed in more detail and a further 451 articles were excluded for the following reasons: unrelated to the study question of the systematic review (n = 113), case reports (n = 97), laparoscopic appendicectomy (n= 2), open vs laparoscopic study (n = 47), review article (n = 43), management of appendicular mass (n = 57), percutaneous appendicular abscess drainage (n = 23), report of experience (n = 20), phlegmonous or catarrhal appendicitis (n = 19), single port surgery (n = 12), technical note (n = 7), pain study (n = 4), survey (n = 3), natural orifice transluminal endoscopic surgery appendicectomy (n = 2), pilot study (n = 1), cost analysis study (n = 1).

The full texts for the remaining 23 articles were assessed by the authors (Gravante G and Overton J) and nine articles were excluded from the qualitative and quantitative analysis for the following reasons: the study included cases of gangrenous and perforated appendicitis managed with all drain types and did not focus on





Figure 1 PRISMA figure showing the results of the search strategy.

the use of intra-abdominal drains placed at the time of surgery (n = 3); the outcomes of the respective groups were not presented separately (n = 2); the study included patients with phlegmonous or catarrhal appendicitis (n = 1), did not specify the numbers of patients allocated to the respective groups (n = 1), included patients managed by transperitoneal drainage (n = 1), or presented outcome data relating to groups according to the type of antibiotic used (n = 1).

Twelve articles presented the outcomes for the usage of intra-abdominal drains in the management of gangrenous and perforated appendicitis by open appendicectomy. These were the studies eligible for inclusion in the systematic review and therefore were included in the quantitative analysis: 6/12 were randomized controlled trials, 6/12 were retrospective case-controlled studies (Figure 1).

RATE OF POSTOPERATIVE INTRA-AB-DOMINAL ABSCESS FORMATION

Rates of postoperative intra-abdominal abscess formation

in open appendicectomy with drainage vs non-drainage were presented in 9/12 studies (5/12 were retrospective case-controlled studies and 4/12 were randomised controlled trials) (Table 1)^[3,11-18]. The overall rate of intraabdominal abscess was more than two times higher in the drainage group (10.3%; 39/378) than in the non-drainage group (4.7%; 37/779, $\chi^2 P < 0.0001$; Table 1)^[3,11-18]. Unfortunately, 2/12 articles span over a long period of time $(1978 \text{ to } 2012)^{[11,18]}$ and 5/12 of them were retrospective case-controlled studies^[3,12,13,16,18]. Studies published before the year 2000 reported an average rate of postoperative intra-abdominal abscess formation of 11.7% in the drainage group (19/163) vas compared with a rate of 6.8% in the non-drainage group $(30/444; \chi^2 \text{ test}, P < 0.05)^{[3,11-14]}$, Studies published after the year 2000 have an average rate of postoperative intra-abdominal abscess formation of 9.3% in the drainage group (20/215) when compared with 2.1% in the non-drainage group (7/335; χ^2 test, P < 0.0001)^[16-18].

RATE OF POSTOPERATIVE ILEUS

Only six studies compared the occurrence of postoperative ileus among the drain *vs* non-drain group and all of them showed higher occurrences of postoperative ileus in the drain one^[5,11,14,17-19]. Overall, the incidence of postoperative ileus was significant higher (more than 2 times) in patients receiving drains: 20.3% (50/246) for the drain group *vs* 8.5% (33/389) for the non-drain group (P <0.0001; Table 1). Similar to what evidenced for the IAAs, early studies had occurrences significant higher than late studies in both groups: 33.3% (40/120 - before 2000) *vs* 7.9% (10/126 - after 2000; χ^2 test, P < 0.001) for the drain group, 20.7% (28/135 - before 2000) *vs* 2.0% (5/254 - after 2000; χ^2 test, P < 0.001) for the non-drain group.

RATE OF SSIS

Eleven (6/11 randomised controlled trials and 5/11 retrospective case-controlled studies) reported the rates of SSIs in the drain (149/458; 32.5%) *vs* non-drains group (112/692; 16.2%)^[3,11,12,14-21]. The risk was two times greater in the drain group compared to the non-drain one (P < 0.0001; Table 1). Early studies had occurrences significant higher than late studies in both groups: 39.0%% (69/177 - before 2000) *vs* 28.5% (80/281- after 2000; χ^2 test, P = 0.02) for the drain group, 22.9% (73/319 - before 2000) *vs* 11.2% (46/409 - after 2000; χ^2 test, P < 0.001) for the non-drain group.

RATE OF OTHER POSTOPERATIVE COM-PLICATIONS

A higher incidence of fecal fistulas^[11,14,17,21] and burst abdomen^[11,14] was also present in the drain *vs* non drain group, however a formal odds ratio could not be calculated due to the absence of events in the non-drain group (Table 1). No significant differences were found among

:	ğ
	ben
	ap
	ous
	len
	ang
•	בי
	d ar
	ate
	rtor
	ad .
	1 0
	ted
	g
	con
	es es
	Mo
	i S S
:	n
	bbe
	en a
	ð
	B
	nag
	llal
	u o
	ي ع
	ge v
	lina
	dra
Ś	S Of
	ect
	eII
	the
	ung
	alyz
	an
:	dle
	stu
	tive
	ara
	duc
(3
	e
	aD
'	

Ref.	Year	Country	Type of study	Type of appendix	Treatment	Patients (<i>n</i>)	Antibiotic regimen	Abdominal abscess	Postoperative ileus	Surgical site infections	Wound dehiscence	Adhesions	Fecal fistula	Burst abdomen	Mortality
Everson et al ^[20]	1977	United Kingdom	RCT	PR/GA	D	14	Cephaloridine 1gr QDS - 3 d coverage			3 (21)					,
					QN	16	Cephaloridine 1gr QDS - 3 d coverage		,	6 (38)	,	,	'		,
Greenall et al ^[11]	1978	United Kingdom	RCT	PR	D	48	(various antibiotics)	7 (15)	18 (38)	34 (71)	,	ı	2 (4)	3 (6)	3 (6)
					QN	55	(various antibiotics)	12 (22)	12 (22)	38 (69)	,	,	0 (0)	0 (0)	1 (2)
MacKellar <i>et al</i> ^{[12}	1986	Australia	Retros.	PR/GA	D	19	Metronidazole ± Gentamycin and Ampicillin (if	1 (5)	,	3 (16)	ı	,		,	,
					Q	139	suspected peritonitis) Metronidazole ± Gentamycin and Ampicillin (if	2 (1)	,	2 (1)					
Samelson <i>et al</i> ^[13]	1987	United States	Retros.	PR	D	24	suspected peritonitis) Ampicillin, Gentamycin and Clindamycin if	3 (13)							
					Ŋ	170	suspected perforation for 7-10 d Ampicillin, Gentamycin and Clindamycin if	3 (2)	,	ı				,	ı
							suspected perforation for 7-10 d								
Dandapat et al ^[14]	1992	India	RCT	PR	Ω	40	,	8 (20)	17 (43)	22 (55) 22 (55)	,	,	2 (5)	2 (5)	4 (10)
Tobaccas of al[3]	1000	Thitad Chatan	Dottood	đđ	n c	6 6	•	10 (22) 0 (0)	13 (28) 5 (16)	23 (50) 1 <i>(</i> 2)		•	0 (0)	0 (0)	1 (2)
	0661	OILIEU JIAIES	Netros.	11	e Q	8 8		0 (0) 3 (9)	3 (9)	1 (3) 2 (5.9)					
Toki et al ^[15]	1995	Japan	RCT	PR	D	24	Aminoglycoside and Cephem	2 (8)		6 (25)	,	0 (0)	,		
					QN	29	Aminoglycoside and Cephem	0 (0)	,	2 (7)	,	0 (0)	,	,	,
Perović <i>et al^[19]</i>	2000	Croatia	Retros.	PR	D	20		ı	4 (20)	13 (65)	2 (10)	ı	,	,	,
					QN	36		ı	1 (3)	7 (19)	2 (6)	ı	,	,	,
Narci et al ^[16]	2007	Turkey	Retros.	PR	D	109		14 (13)		31 (28)	·	3 (3)			
					QZ	117		4 (3)	,	19 (16)	·	4 (3)	,	,	,
Jani <i>et al^[17]</i>	2011	Kenya	RCT	PR	D	45	Cefuroxime and Metronidazole or Penicillin,	3 (7)	1 (2)	15 (33)			2 (4)	·	
							Gentamicin and Metronidazole or Amoxicillin-								
							Clavulanate and Metronidazole								
					Q	45	Cefuroxime and Metronidazole or Penicillin,	0 (0)	0 (0)	3 (7)	·	ı	0 (0)	ı	ı
							Gentamicin and Metronidazole or Amoxicillin- Clavulanate and Metronidazole								
Akkovun <i>et al</i> ^[18]	2012	Turkev	Retros.	РК	0	61		3 (5)	5 (8)	3 (5)	1 (2)	1 (2)	,	,	,
					QN	173		3 (2)	4 (2)	3 (2)	0 (0)	1 (1)			
Al-Shahwany	2012	Iraq	RCT	PR	D	46	Ceftriaxone and Metronidazole	1		18 (39)			0 (0)	,	0 (0)
et al ^[21]					QN	38	Ceftriaxone and Metronidazole			14 (37)	·		0 (0)	,	0 (0)
Total					D	482		39/378 (10.3)	50/246 (20.3)	149/458 (32.5)	3/81 (3.7)	4/194(2)	6/179 (3.4)	5/88 (5.7)	7/134 (5.2)
					QN	862		37/779 (4.7)	33/389 (8.5)	112/692 (16.2)	2/209 (0.95)	5/319 (1.6)	0/184(0)	0/101 (0)	2/139 (1.4)
Power calculatio.	Ę							80%	95%	%66	1%	0.02%	, %66	%66	%66
odds ratio P value (D 75 ND	Ę							2.2 < 0.0001	2.4 < 0.0001	2 < 0.0001	3.9 0.11 (NS)	1.3 0.68 (NS)	- 10 0	- 100	3.7 0.08 (NIS)
The second second								100000	100000	100000	(01) 11:0		10:0	10.0	

Gravante G et al. Intraperitoneal drains during open appendicectomy



¹Although the incidence was higher in the drain zs non drain group, the odds ratio could not be formally calculated for this complication because of the lack of occurrences in the latter. PR: Perforated appendix; GA: Gangrenous appendix; D: Drainage; ND: Non drainage; RCT: Retrospective randomised trial; Retros.: Retrosc.: Retrosc.:

groups for the mortality rate (7/134, 5.2% vs 2/139, 1.4%; P = 0.08)^[11,14,21] (Table 1). With regards to the incidence of wound dehiscences^[18,19] and bowel obstruction due to adhesions^[15,16,18] the data were underpowered to produce reliable result in terms of significant differences among groups (Table 1).

OTHER OUTCOMES

Two retrospective case-controlled studies reported that overall operative times were 8 min longer in the drainage group as compared with the non-drainage group^[16,18]. Four articles (2 retrospective case-controlled studies and 2 randomised controlled studies) reported longer length of hospital stay in the drainage group as compared with the non-drainage group^[3,15,18,21].

CRITICAL EVALUATION

Appendicectomy is the most common emergency operation performed in abdominal surgery. Generally considered a technically simple procedure, the variability of the intraoperative findings (normal appendix, perforated appendix, presence of IAA or widespread peritonitis, appendicular mass, retrocecal appendix, involvement of the terminal ileum mesentery)^[22-24] coupled with the patient's characteristics (*i.e.*, extremes of age, pregnancy, obesity, comorbidities)^[25-27] and the approach used (open, laparoscopic, single incision, natural orifice surgery)^[28], may increase the technical difficulties and therefore challenge even experienced surgeons. The incidence of postoperative complications differs significantly according to the stage of the disease. Simple appendicitis is when the appendix presents macroscopically normal and the inflammatory infiltrate, if present, is confined mainly to the mucosa (35% of total cases), or when the appendix is macroscopically indurated or purulent and the histological analysis shows mucosal necrosis and transmural inflammation (36% of cases)^[29]. In these cases the incidence of postoperative complications is relatively low: SSIs are present in 8.5% of patients $(272/3196)^{[30-40]}$, IAAs in 0.4% $(13/3196)^{[30-40]}$, and bowel obstruction due to adhesions in 0.5% (10/1853)^[31,32,34,38,39,41]. Differently, gangrenous and perforated appendicitis is when the appendix presents macroscopically gangrenous with part or whole of the appendix necrotic (9% of cases) or perforated with peritonitis (20% of cases)^[29]. In these cases the incidence of complications is higher: SSIs are present in 22.6% of patients (268/1186)^[3,11,12,14-21], IAAs in 6.4% $(78/1210)^{[3,11-18]}$, and bowel obstruction due to adhesions in 1.8% (9/513)^[15,16,18].

The insertion of intraperitoneal drains during appendicectomies in cases of perforated appendicitis is meant to prevent the formation of IAAs in the early postoperative period. The idea is based on the significant amount of bacterial contamination usually found during the operation that originated from the perforation of the hollow viscus. Following the appendix removal

(source of the contamination) and an adequate wash-out of the abdominal cavity (mechanically removal of the contaminated fluid), the insertion of an intraperitoneal drain is meant to continuously aspirate any contaminated pollution leftover that could eventually re-start a local infection. At the same time the patient usually receives an appropriate perioperative course of antibiotic therapy to definitely sterilize the abdominal cavity. If the assumption that drains remove infected fluids and allow the antibiotics a more efficacious action is true, the incidence of postoperative IAAs should be inferior in patients receiving drains vs those that do not. Studies available have a significant degree of data heterogeneity with regards to age, co-morbidities, time of presentation to the hospital, type of antibiotic used when considering studies conducted before the year 2000 and those conducted after (including some which are rarely used, i.e., tetracycline, colomycin, streptomycin)^[11], the amount of wash-out of the abdominal cavity performed, and the experience of the surgeon. Bearing in mind these limitations some important points can still be made. With the exception of for Greenall *et al*^{11]} in which the occurrence of abscesses was less in the drainage group than compared to the non-drainage group, 6/12 studies reported higher rates of intra-abdominal abscesses^[12,13,15-18] and 2/12 reported comparable rates of intra-abdominal abscesses between the respective groups^[3,14]. These reported outcomes demonstrate that the rates of postoperative intra-abdominal abscess formation are lower in the non-drainage group as compared with the drainage group irrespective of the time period during which the study was conducted. Therefore, when considering the rate of intra-abdominal abscess formation reported in early studies (i.e., those published before the year 2000) as compared with those from late studies (*i.e.*, those published after the year 2000) the rate has remained similar in the drainage group among early vs late studies $(19/163 \text{ vs } 20/215, \chi^2 \text{ test}, P = \text{NS})$, while it significantly decreased in the non-drainage group (30/444 vs 7/335, γ^2 test, P < 0.001).

Simple guidelines for the use of drains according to the intraoperative findings cannot be easily drawn and a large role in these cases is actually played by the personal experience and practice. When IAAs are still not formed and the intraoperative findings are those of free pus, a prolonged and abundant irrigation with large amounts of normal saline solution accompanied by a thorough aspiration until the washing liquid is completely clear are frequently sufficient manoeuvres to remove most of the infected material. The abundant wash-out of the abdominal cavity removes the "bulk" of the contamination and facilitates the task for perioperative antibiotics to sterilise the remaining pollution. A careful irrigation is also necessary to remove fecaliths located in remote regions which are not easily accessible by direct exploration (i.e., subphrenic, Douglas, interloop) and in which IAAs are more likely to form^[42]. Such areas may require positional changes (i.e., Trendelemburg, anti-Trendelemburg, right- or left-sided positions) or using the drain shelf to introduce and aspirate the washing liquid in such remote regions. However, it is the authors opinion that when the IAA is completely formed the aspiration of pus leaves an infected cavity that may create an adequate isolated environment for a local recurrence. We believe that if the abscess wall can be adequately removed from the surfaces of the bowel, omentum, and peritoneum then a drain is likely to be superfluous and a thorough irrigation will suffice. However, in cases of incomplete removal, difficult dissection or oozing from raw surfaces a tube drain might be useful to prevent postoperative IAAs. No study has investigated this possibility so far.

The effects of drains manifest also on the occurrence of postoperative ileus and SSIs. Postoperative ileus could be associated to the presence of intraperitoneal drain for a direct irritant effect of the drain on the bowel serosa and consequently the recovery of peristalsis, or for an indirect effect of reduced mobilisation of the patient due to the drain^[6]. With regards to SSI, the same considerations of heterogeneity that were observed for the analysis of IAAs can also be applied here. This heterogeneity is reflected in the wide range of reported rates of SSIs (1% to 71%). Rates were 3%-71% in the drainage group and 1%-69% in the non-drainage group (Table 1) but were reportedly lower in the non-drainage group for 9 out of 12 studies presented, suggesting that intra-abdominal drains may represent an independent risk factor for the development of SSIs. A simple explanation to this phenomenon is found in the rare eventuality that drain are exteriorised directly through the main surgical wound, a manoeuvre used to avoid additional wounds in the abdominal wall. In such cases wounds tend to contaminate quickly due to the direct link between the septic intrabdominal focus and the abdominal wall operated by the drain itself. The purulent exudates travel by capillarity not only within the lumen but also on the outer surface of the drain where they easily come into contact with the main wound and start a new infection. For these reasons it is common surgical practice not to drain the infected abdominal cavities through the main wound but to perform a new different one where the drain is exteriorised. When reported, the drainage was operated through a separated wound in most studies^[12,15,17], through the same wound in others^[20], or the decision was left to the operating surgeon^[11]. Therefore, it is still possible that SSIs originate from the direct communication between the intra-abdominal cavity and the external skin surface operated by the outer surface of the drain even when this is exteriorised through separate wounds close to the main one.

CONCLUSION

The prophylactic use of intraperitoneal drains for gangrenous or perforated appendicitis remains a contentious issue, particularly in the context of enhanced recovery programs that frequently exclude their usage. Considering the management of gangrenous or perforated appendicitis by open appendicectomy, all but one study failed to demonstrate any reduction in the rate of postoperative complications and the majority of them found higher incidences associated with the use of drains.

REFERENCES

- Robinson JO. Surgical drainage: an historical perspective. Br J Surg 1986; 73: 422-426 [PMID: 3521783 DOI: 10.1002/ bjs.1800730603]
- 2 Yates JL. An experimental study of the local effects of peritoneal drainage. Am Surg 1955; 21: 1048-1072 [PMID: 13259118]
- 3 Johnson DA, Kosloske AM, MacArthur C. Perforated appendicitis in children: to drain or not to drain? *Pediatr Surg Int* 1993; 8: 402-405 [DOI: 10.1007/BF00176728]
- 4 Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T. Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis. *Colorectal Dis* 2006; 8: 259-265 [PMID: 16630227 DOI: 10.1111/ j.1463-1318.2006.00999.x]
- 5 Urbach DR, Kennedy ED, Cohen MM. Colon and rectal anastomoses do not require routine drainage: a systematic review and meta-analysis. *Ann Surg* 1999; 229: 174-180 [PMID: 10024097 DOI: 10.1097/00000658-199902000-00003]
- 6 Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, McNaught CE, MacFie J, Liberman AS, Soop M, Hill A, Kennedy RH, Lobo DN, Fearon K, Ljungqvist O. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr* 2012; **31**: 783-800 [PMID: 23099039 DOI: 10.1016/j.clnu.2012.08.013]
- 7 Gravante G, Elmussareh M. Enhanced recovery for colorectal surgery: Practical hints, results and future challenges. *World J Gastrointest Surg* 2012; 4: 190-198 [PMID: 23293732 DOI: 10.4240/wjgs.v4.i8.190]
- 8 Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, von Meyenfeldt MF, Fearon KC, Revhaug A, Norderval S, Ljungqvist O, Lobo DN, Dejong CH. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009; **144**: 961-969 [PMID: 19841366 DOI: 10.1001/archsurg.2009.170]
- 9 Weeden WM. The gibson-mikulicz drain in acute appendicitis: with report of 1588 cases. *Ann Surg* 1928; 88: 76-79 [PMID: 17865925 DOI: 10.1097/00000658-192807000-00009]
- 10 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed)* 2009; 339: b2535
- 11 Greenall MJ, Evans M, Pollock AV. Should you drain a perforated appendix? Br J Surg 1978; 65: 880-882 [PMID: 737427 DOI: 10.1002/bjs.1800651215]
- 12 MacKellar A, Mackay AJ. Wound and intraperitoneal infection following appendicectomy for perforated or gangrenous appendicitis. *Aust N Z J Surg* 1986; 56: 489-491 [PMID: 3460560 DOI: 10.1111/j.1445-2197.1986.tb02361.x]
- 13 Samelson SL, Reyes HM. Management of perforated appendicitis in children-revisited. Arch Surg 1987; 122: 691-696 [PMID: 3579584 DOI: 10.1001/arch-surg.1987.01400180073014]
- 14 Dandapat MC, Panda C. A perforated appendix: should we drain? J Indian Med Assoc 1992; 90: 147-148 [PMID: 1522303]
- 15 Toki A, Ogura K, Horimi T, Tokuoka H, Todani T, Watanabe Y, Uemura S, Urushihara N, Noda T, Sato Y. Peritoneal lavage versus drainage for perforated appendicitis in children. *Surg Today* 1995; 25: 207-210 [PMID: 7640447 DOI: 10.1007/BF00311528]
- 16 Narci A, Karaman I, Karaman A, Erdoğan D, Cavuşoğlu YH, Aslan MK, Cakmak O. Is peritoneal drainage necessary in childhood perforated appendicitis?--a comparative study.



J Pediatr Surg 2007; **42**: 1864-1868 [PMID: 18022437 DOI: 10.1016/j.jpedsurg.2007.07.013]

- 17 **Jani PG**, Nyaga PN. Peritoneal Drains in Perforated Appendicitis without Peritonitis: A Prospective Randomized Controlled Study. *East Cent Afr J Surg* 2011; **16**: 62-71
- 18 Akkoyun I, Tuna AT. Advantages of abandoning abdominal cavity irrigation and drainage in operations performed on children with perforated appendicitis. *J Pediatr Surg* 2012; 47: 1886-1890 [PMID: 23084202 DOI: 10.1016/ j.jpedsurg.2012.03.049]
- Perovic Z. [Drainage of the abdominal cavity and complications in perforating appendicitis in children]. *Med Pregl* 2000; 53: 193-196 [PMID: 10965688]
- 20 Everson NW, Fossard DP, Nash JR, Macdonald RC. Wound infection following appendicectomy: the effect of extraperitoneal wound drainage and systemic antibiotic prophylaxis. *Br J Surg* 1977; 64: 236-238 [PMID: 322787 DOI: 10.1002/ bjs.1800640403]
- 21 Al-Shahwany IW, Hindoosh LN, Rassam R, Al-Qadhi A. Drain or not to drain in appendectomy for perforated appendicitis. *Iraqi Postgrad Med J* 2012; 11: 349-353
- 22 Mason RJ, Moazzez A, Sohn H, Katkhouda N. Metaanalysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012; **13**: 74-84 [PMID: 22364604 DOI: 10.1089/sur.2011.058]
- 23 Markides G, Subar D, Riyad K. Laparoscopic versus open appendectomy in adults with complicated appendicitis: systematic review and meta-analysis. *World J Surg* 2010; 34: 2026-2040 [PMID: 20549210 DOI: 10.1007/s00268-010-0669-z]
- 24 Markar SR, Blackburn S, Cobb R, Karthikesalingam A, Evans J, Kinross J, Faiz O. Laparoscopic versus open appendectomy for complicated and uncomplicated appendicitis in children. J Gastrointest Surg 2012; 16: 1993-2004 [PMID: 22810297 DOI: 10.1007/s11605-012-1962-y]
- 25 Woodham BL, Cox MR, Eslick GD. Evidence to support the use of laparoscopic over open appendicectomy for obese individuals: a meta-analysis. *Surg Endosc* 2012; 26: 2566-2570 [PMID: 22437955 DOI: 10.1007/s00464-012-2233-4]
- 26 Southgate E, Vousden N, Karthikesalingam A, Markar SR, Black S, Zaidi A. Laparoscopic vs open appendectomy in older patients. *Arch Surg* 2012; 147: 557-562 [PMID: 22786544 DOI: 10.1001/archsurg.2012.568]
- 27 Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A. Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. *Br J Surg* 2012; **99**: 1470-1478 [PMID: 23001791 DOI: 10.1002/bjs.8889]
- 28 Gill RS, Shi X, Al-Adra DP, Birch DW, Karmali S. Singleincision appendectomy is comparable to conventional laparoscopic appendectomy: a systematic review and pooled analysis. Surg Laparosc Endosc Percutan Tech 2012; 22: 319-327

[PMID: 22874680 DOI: 10.1097/SLE.0b013e31824f2cf8]

- 29 Carr NJ. The pathology of acute appendicitis. Ann Diagn Pathol 2000; 4: 46-58 [PMID: 10684382 DOI: 10.1016/S1092-9134(00)90011-X]
- 30 **Minhas Q**, Siddique K, Mirza S, Malik AZ. Post-Operative Complications of Stump Ligation Alone Versus Stump Ligation with Invagination in Appendicectomy. *IJS* 2010; **22**: 1
- 31 Watters DA, Walker MA, Abernethy BC. The appendix stump: should it be invaginated? *Ann R Coll Surg Engl* 1984; 66: 92-93 [PMID: 6703637]
- 32 Sinha AP. Appendicectomy: an assessment of the advisability of stump invagination. *Br J Surg* 1977; **64**: 499-500 [PMID: 922311 DOI: 10.1002/bjs.1800640714]
- 33 Lavonius MI, Liesjärvi S, Niskanen RO, Ristkari SK, Korkala O, Mokka RE. Simple ligation vs stump inversion in appendicectomy. *Ann Chir Gynaecol* 1996; 85: 222-224 [PMID: 8950444]
- 34 Khan S. Assessment of stump invagination versus simple ligation in open appendicectomy. *JIOM* 2010; **32**: 7-10
- 35 Khan N, Bangash A, Mushtaq M, Din Sadiq MU, Muhammad I. Simple ligation versus ligation and burial of stump in appendicectomy in patients with clinical diagnosis of acute appendicitis. *JPMI* 2009; 23: 74-80
- 36 Jamal A, Tariq M, Khan MA, Ayyaz M. Comparison of two surgical techniques; simple ligation and ligation with invagination of appendicular stump in appendicectomy for acute appendicitis. Pak J Med Health Sci 2012. Available from: URL: http://pjmhsonline.com/Comparison%20of%20two% 20Surgical%20Techniques;%20Simple%20Ligation%20and% 20Ligation.htm
- 37 Engström L, Fenyö G. Appendicectomy: assessment of stump invagination versus simple ligation: a prospective, randomized trial. *Br J Surg* 1985; 72: 971-972 [PMID: 3910160 DOI: 10.1002/bjs.1800721212]
- 38 Chaudhary IAS, Mallhi AA, Afridi Z, Bano A. Is it necessary to invaginate the stump after appendicectomy? *Pak J Med Sci* 2005; 21: 35-38
- 39 Chalya PL, Mchambe M. Is Invagination of Appendicular Stump in Appendicectomy Necessary? A Prospective Randomized Clinical Study. *East Cent Afr J Surg* 2012; 17: 85-88
- 40 **Amirian GR**, Hydari MB, Rezaei M. Comparison of simple legation of the appendix with purse string diving appendectomy complication. *Behbood J* 2011; **15**: 107-111
- 41 Street D, Bodai BI, Owens LJ, Moore DB, Walton CB, Holcroft JW. Simple ligation vs stump inversion in appendectomy. *Arch Surg* 1988; 123: 689-690 [PMID: 3285806 DOI: 10.1001/archsurg.1988.01400300031003]
- 42 Abularrage CJ, Bloom S, Bruno DA, Goldfarb A, Abularrage JJ, Chahine AA. Laparoscopic drainage of postappendectomy- retained fecalith and intra-abdominal abscess in the pediatric population. *J Laparoendosc Adv Surg Tech A* 2008; 18: 644-650 [PMID: 18721024 DOI: 10.1089/lap.2007.0190]

P- Reviewers: Augustin G, Costi R, Elsandabesee E S- Editor: Song XX L- Editor: A E- Editor: Zhang DN





WJSP www.wjgnet.com



World Journal of **Surgical Procedures**

Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.5412/wjsp.v3.i3.25 World J Surg Proced 2013 November 28; 3(3): 25-28 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

MINIREVIEWS

Retroileal trans-mesenteric colorectal anastomosis

Pierpaolo Sileri, Ilaria Capuano, Carolina Ilaria Ciangola, Luana Franceschilli, Federica Giorgi, Achille Lucio Gaspari

Pierpaolo Sileri, Ilaria Capuano, Carolina Ilaria Ciangola, Luana Franceschilli, Federica Giorgi, Achille Lucio Gaspari, Department of Surgical Sciences, University of Rome Tor Vergata, 00133 Rome, Italy

Author contributions: All authors contributed to substantial contributions to conception and design, acquisition of data; Sileri P, Capuano I and Franceschilli L contributed to drafting the article or revising it critically for important intellectual content; Sileri P, Capuano I and Gaspari AL gave final approval of the version to be published.

Correspondence to: Pierpaolo Sileri, MD, MS, PhD, Department of Surgical Sciences, University of Rome Tor Vergata, Cattedra Chirurgia Generale, Policlinico Tor Vergata, 6B, Viale Oxford 81, 00133 Rome, Italy. piersileri@yahoo.com Telephone: +39-33-39137249 Fax: +39-6-20902927

Received: August 17, 2013 Revised: October 22, 2013 Accepted: November 7, 2013 Published online: November 28, 2013

Abstract

Colorectal anastomosis after extended left colectomies may result difficult, and, sometimes, impossible due to the shortness of the vascular pedicles and the distance between the two ends. Total colectomy with ileo-rectal or ileo-anal anastomosis with sacrifice of healthy colon and ileocaecal valve is usually preferred to overcome this problem. In this manuscript we describe the stepby-step surgical technique of retroileal transmesenteric colorectal anastomosis which can be used as a salvage technique for both open and laparoscopic surgeries. We also discuss the advantages and disadvantages of this approach compared to other techniques. We believe that the widespread of laparoscopic colorectal surgery as well as the raising volume of metachronous colorectal resections will revive this vintage overlooked approach.

 $\ensuremath{\mathbb{C}}$ 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Colorectal anastomosis; Retroileal anasto-

mosis; Extended left colectomy

Core tip: Several approaches have been proposed as salvage techniques to avoid total colectomy with ileorectal or ileo-anal anastomosis after an extensive mobilization and left colon resection. However, as these techniques, which we are going to discuss hereafter, involve various technical difficulties, we present a valid alternative to ileo-rectal or ileo-anal anastomosis: a retro-ileal, trans-mesenteric colorectal anastomosis, first described by R. Turnbull in 1972, which allows a safe and tension free anastomosis after both open and laparoscopic extended left colon resections with inadequate residual length for standard colo-rectal anastomosis.

Sileri P, Capuano I, Ciangola CI, Franceschilli L, Giorgi F, Gaspari AL. Retroileal trans-mesenteric colorectal anastomosis. *World J Surg Proced* 2013; 3(3): 25-28 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/25.htm DOI: http:// dx.doi.org/10.5412/wjsp.v3.i3.25

INTRODUCTION

After extensive mobilization and left colon resection, the colorectal anastomosis may result impossible due to the distance between the two ends and the shortness of the middle and right colic pedicles. Several approaches have been proposed as salvage techniques to avoid total colectomy with ileo-rectal or ileo-anal anastomosis in these cases. It is well known that low colo-rectal anastomosis may have septic complications as high as 15%, while ileorectal anastomosis may have a risk of anastomotic leak between 3%-17%^[1,2]. It is obvious that the aim of surgery should be to preserve the function (*i.e.*, ileo-caecal valve and a portion of the colon) as well as reduce complications (i.e., anastomotic leak or septic complications). In particular, when an ileo-rectal anastomosis is avoided, the terminal ileum and the ileo-caecal valve preservation reduces malabsorption, bacterial overgrowth, while improv-



ing diarrhoea, urgency or incontinence, usually occurring after extended colonic resection. Over the last decades few approaches have been described mainly in the open surgery era.

The Deloyers^[3] procedure, consisting in an anastomosis between the right or the transverse colon and the rectum or anus after mobilizing and rotating into a counter clockwise direction the right colon (including the caecum and the ascending colon, up to the hepatic flexure) with preservation of the ileo-colic junction and the ileocolic artery. After the initial Deloyers' report only 5 studies, including less than 100 patients have shown good functional results mainly after surgery for chronic constipation or Hirschprung disease^[4-6]. Among these, only one paper considered this approach after Hartmann reversal, failed previous colorectal anastomosis, diverticular disease, left colon cancer and ischemic colitis. This retrospective study observed the largest population (48 patients), reporting early complications up to 23% (mainly intra-abdominal haemorrhage, wound infection, persistent ileus) and 23% of late complications (incisional hernias, colo-anal anastomosis stenosis)^[7].

Subtotal colectomy with caeco-rectal end-to-end anastomosis, when the right colon can not be preserved. This technique seems, however, to be comparable to the total colectomy with ileo-rectal anastomosis technique in terms of therapeutic effectiveness, postoperative morbidity and mortality and impact on the quality of life^[8].

Moreover, these two approaches may present several technical difficulties when a laparoscopic approach is needed. Obviously, the widespread of laparoscopic colorectal surgery demands for faster and easier techniques.

In 1972, Turnbull proposed a retro-ileal tunnel to anastomose the proximal transverse colon to the rectum. This technique consists in performing a passage through an avascular plan at the terminal ileum mesentery and the proximal transverse colon, anastomosed to the rectum. However, this old technique has been largely overlooked for decades, although it represents a valid alternative to ileo-rectal or ileo-anal anastomosis, allowing a safe and tension free anastomosis. Since it is very easy to perform, we believe that this is the technical solution for both open and laparoscopic extended left colon resections with inadequate residual length for standard colo-rectal anastomosis.

In the manuscript we present the surgical technique with a series of figures suitable either for open or laparoscopic approach.

SURGICAL TECHNIQUE DESCRIPTION

Ileal mesentery window creation

After extended left colectomy, the remnant colon is vascularized only by the tributaries of the superior mesenteric artery. The entire small intestine is retracted on the left side of the patient and cranially, in order to expose the root of the mesentery. At this point, the terminal ileum is identified for a segment of 30-50 cm and the mesentery is inspected for the vascular arcades. This allows the respect of the terminal ileum and caecum vascularization when the window is created and tailored for the transverse colon passage. Usually, a 3 cm opening is necessary (Figure 1A). While in open surgery a transmesenteric lighting, in order to individualize the avascular plane, is possible, during laparoscopic surgery this is not doable, since the light is in the same direction of the scope. However, the window can be created immediately proximal to the take-off of the ileo-colic vessel, where an avascular plane is usually present.

Freeing the transverse colon

It is necessary to free the transverse colon from its attachments, particularly from the gastro-colic ligament as well as all the folds that may create tension thus creating tension through the mesenteric passage. The distance that needs to be covered can be measured above the mesentery. If a laparoscopic approach is used and a mechanical anastomosis is planned, the anvil is inserted after a standard purse-string is performed. After the colon has been passed through the avascular mesenteric window (Figure 1B), the anastomosis is performed. If an open technique is chosen an end-to-end or side-to-end anastomosis is performed. At this point the anvil is gently passed through the mesentery and the anastomosis performed to the rectal stump. Once these two elements have been connected, an anastomosis is performed and checked, to ensure that there is no tension or twisting (Figure 1C). Finally, the colon is fixed to the border of the mesenteric passage using interrupted absorbable 2-0 stitches and the posterior mesenteric window (or residual gap) is closed with interrupted stitches to avoid internal hernias.

Our experience

Since 2007 we have performed this procedure in 10 patients. All patients were male with a mean age of 65.1 years (range: 41-82 years). Indications for surgery were: left colon cancer (n = 2), left colon cancer associated with diverticular disease (n = 2), metachronous left colorectal cancer in previously resected patients (n = 2), synchronous cancer of the recto-sigmoid colon and the splenic flexure (n = 2), extensive diverticular disease (n = 2). Of these surgeries, 8 were open while 2 were laparoscopic. Median follow up was 40 mo. One patient had superficial Surgical Site Infection. One patient developed an incisional hernia on the site of 15 mm trocar insertion, repaired 6 mo after surgery. Three patients experienced longer term diarrhoea, and 2 of them required occasional Loperamide treatment. One patient died 2 mo after surgery due to sequelae of his Chronic Renal Failure. He had a previous failed renal transplant, secondary to acute rejection. Two patients died due to cancer recurrence, 2 and 4 years after surgery, respectively. No complications related to the surgical procedures were encountered, including anastomotic leaks, stenosis or small bowel obstruction secondary to internal hernia or adhesions.





Figure 1 leal mesentery surgical technique description. A: After the proximal resection, an avascular mesenteric window is created; B: After an extended left colectomy has been performed, the remnant colon is passed through the avascular mesenteric window, behind the ileum; C: An end-to-end, trans-mesenteric, retroileal colo-rectal anastomosis is performed.

DISCUSSION

We believe that this "vintage" technique has been overlooked for decades and it may turn to be fashion again after the widespread of colorectal laparoscopy. Major drawbacks such as the need of proximal transverse colon taking down and risk of internal hernia through the mesenteric window or jejunum loop obstruction favoured the Deloyers procedure. However, literature on trans-mesenteric lowering is scant^[9-11]. The first Turnbull's report presented 11 retroileal colo-rectal anastomosis with a total of 3 minor postoperative complications, including partial small bowel obstructions resolved medically, 1 small incisional hernia and minor wound infection. For more than 20 years the technique was not presented and reappeared in the literature in 1994 when Nafe et $al^{[10]}$ reported a series of 28 cases with a single case of anastomotic leak (about 3%) comparable to conventional anastomosis. Overall, including sporadic case reports, a handful of reports are present in literature with a lack of surgical indications, specific surgical technique description as well as outcomes.

Supporters of the Deloyers procedure aimed that the retro-ileal anastomosis requires the preservation of the entire transverse colon. Obviously, the ligation of the left branch of the middle colic pedicle is often sufficient, but, if a more extended resection is required with a proximal transverse colon anastomosis, the middle colic pedicle ligation is possible at the origin but, in this case, the sole Drummond's arcade will supply the right transverse co-lon. Regarding the risk of jejunum loop obstruction or the risk of internal hernia through the mesenteric window and performing mesenteric-to-bowel sutures^[9]. Moreover, according to our experience, since the peritoneal window is performed 20-30 cm from the ileo-cecal

valve, proximal to the marginal arcade, this does not represent a limit, when a loop diverting ileostomy is needed.

On the other hand, the Deloyers procedure has the main disadvantage of creating torsion of the vascular pedicle increasing the risk of venous ischemia, despite few modifications have been proposed^[12-14].

Moreover, when a laparoscopic approach is chosen, the retroileal passage seems to be a valid option to overcome the distance between the two ends and to perform a safe, tension-free anastomosis. It is intuitive that a distance between the proximal transverse colon and the rectal stump is less when the intestine crosses the mesenteric route on the right side, through the peritoneal window. In fact, anatomically, the small bowel mesentery from its origin goes mainly from the middle to the left side, leaving the right part to the right colon mesentery. The passage of the colon above the small bowel may result impossible and may jeopardize the vascularization, creating tension. However, the retroileal window may result more difficult in laparoscopic surgery, especially in obese patients, thus a more careful identification of the ileo-colic vessels should be performed. In conclusion, we do believe that this technique can be always used, when an extended left colon resection is required.

REFERENCES

- Chambers WM, Mortensen NJ. Postoperative leakage and abscess formation after colorectal surgery. *Best Pract Res Clin Gastroenterol* 2004; 18: 865-880 [PMID: 15494283]
- 2 Tang ST, Yang Y, Wang GB, Tong QS, Mao YZ, Wang Y, Li SW, Ruan QL. Laparoscopic extensive colectomy with transanal Soave pull-through for intestinal neuronal dysplasia in 17 children. *World J Pediatr* 2010; 6: 50-54 [PMID: 20143211 DOI: 10.1007/s12519-010-0006-5]
- 3 **Deloyers L**. [Suspension of the right colon permits without exception preservation of the anal sphincter after extensive

colectomy of the transverse and left colon (including rectum). Technic -indications- immediate and late results]. *Lyon Chir* 1964; **60**: 404-413 [PMID: 14167748]

- 4 **Prévot J.** [Hirschsprung's disease: Deloyers' technic]. *Ann Chir Infant* 1970; **11**: 81-84 [PMID: 5526530]
- 5 Costalat G, Garrigues JM, Didelot JM, Yousfi A, Boccasanta P. [Subtotal colectomy with ceco-rectal anastomosis (Deloyers) for severe idiopathic constipation: an alternative to total colectomy reducing risks of digestive sequelae]. *Ann Chir* 1997; 51: 248-255 [PMID: 9297887]
- 6 Bonnard A, de Lagausie P, Leclair MD, Marwan K, Languepin J, Bruneau B, Berribi D, Aigrain Y. Definitive treatment of extended Hirschsprung's disease or total colonic form. *Surg Endosc* 2001; **15**: 1301-1304 [PMID: 11727138 DOI: 10.1007/s004640090092]
- 7 Manceau G, Karoui M, Breton S, Blanchet AS, Rousseau G, Savier E, Siksik JM, Vaillant JC, Hannoun L. Right colon to rectal anastomosis (Deloyers procedure) as a salvage technique for low colorectal or coloanal anastomosis: postoperative and long-term outcomes. *Dis Colon Rectum* 2012; 55: 363-368 [PMID: 22469806 DOI: 10.1097/DCR.0b013e3182423f83]
- 8 Marchesi F, Sarli L, Percalli L, Sansebastiano GE, Veronesi L, Di Mauro D, Porrini C, Ferro M, Roncoroni L. Subtotal colectomy with antiperistaltic cecorectal anastomosis in the treatment of slow-transit constipation: long-term impact on qual-

ity of life. *World J Surg* 2007; **31**: 1658-1664 [PMID: 17541684 DOI: 10.1007/s00268-007-9111-6]

- 9 Rombeau JL, Collins JP, Turnbull RB. Left-sided colectomy with retroileal colorectal anastomosis. *Arch Surg* 1978; 113: 1004-1005 [PMID: 687079 DOI: 10.1001/arch-surg.1978.01370200098020]
- 10 Nafe M, Athanasiadis S, Köhler A. [Indications and technique of retro-ileal colorectal anastomosis after expanded left-sided hemicolectomy]. *Chirurg* 1994; 65: 804-806 [PMID: 7995091]
- 11 Hogan NM, Joyce MR. Retroileal colorectal anastomosis: an old technique, still relevant. *Tech Coloproctol* 2012; Epub ahead of print [PMID: 22398845 DOI: 10.1007/ s10151-012-0814-9]
- 12 Roncoroni L, Sarli L, Costi R, Violi V. [Caecal-rectal antiperistaltic anastomosis without torsion of the vascular pedicle]. *Ann Chir* 2000; 125: 871-873 [PMID: 11244595 DOI: 10.1016/ S0003-3944(00)00010-9]
- 13 Perrier G, Peillon C, Testart J. [Modifications of the Deloyers procedure in order to perform a cecal-rectal anastomosis without torsion of the vascular pedicle]. *Ann Chir* 1999; 53: 254 [PMID: 10339871]
- 14 Zinzindohoué F. [Difficult colo-colonic or colo-rectal anastomoses: trans-mesenteric anastomoses and anastomoses with right colonic inversion]. Ann Chir 1998; 52: 571-573 [PMID: 9752509]

P- Reviewers: Cho A, Kin T, Lin JK, Piccinni G S- Editor: Song XX L- Editor: A E- Editor: Zhang DN







Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.5412/wjsp.v3.i3.29

N Û .

World J Surg Proced 2013 November 28; 3(3): 29-36 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

MINIREVIEWS

Platelet therapy: A novel strategy for liver regeneration, anti-fibrosis, and anti-apoptosis

Kazuhiro Takahashi, Soichiro Murata, Nobuhiro Ohkohchi

Japan. nokochi3@md.tsukuba.ac.jp

 Telephone: +81-29-8533221
 Fax: +81-29-8533222

 Received: June 6, 2013
 Revised: August 10, 2013

 Accepted: September 14, 2013
 Published online: November 28, 2013

Abstract

Platelets contain bio-physiological substances, including insulin-like growth factor-1, vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, serotonin, transforming growth factor- β , adenosine diphosphate, adenosine tri-phosphate, and epidermal growth factor. Platelets have conventionally been considered to exacerbate the inflammatory response and liver injury. Recently, platelets were discovered to have a positive impact on the liver. In this review, we present experimental and clinical evidence indicating that platelets accelerate liver regeneration and have anti-fibrosis and antiapoptosis activity, and we detail the mechanisms of action. Platelets accelerate liver regeneration by three different mechanisms: (1) a direct effect on hepatocytes, (2) a cooperative effect with liver sinusoidal endothelial cells, and (3) a collaborative effect with Kupffer cells. Platelets exert anti-fibrotic activity by deactivating hepatic stellate cells via the adenosinecyclic adenosine 5'-monophosphate signaling pathway. Platelets prevent hepatocyte apoptosis by activating the Akt pathway and up-regulating Bcl-xL, which suppresses caspase-3 activation. Platelet therapy with thrombopoietin, thrombopoietin receptor agonists, and platelet transfusion has the advantages of convenience and cost-efficiency over other treatments. We propose that in the future, platelet therapy will play a promising role in the treatment of the various liver disorders that currently challenge the surgical field, such as liver failure after a massive hepatectomy, hepatectomy of a cirrhotic liver, and small grafts in liver transplantation.

 $\ensuremath{\mathbb{C}}$ 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Platelet therapy; Liver regeneration; Liver fibrosis; Hepatocyte apoptosis; Growth factor

Core tip: Platelets have conventionally been considered to exacerbate the inflammatory response and liver injury. Recently, some studies have demonstrated a role for platelets in promoting liver regeneration, improving liver fibrosis, and attenuating hepatitis. In this review, the experimental and clinical evidence that platelets accelerate liver regeneration and attenuate fibrosis and apoptosis are described, as are the mechanisms of action. Platelet therapies, such as thrombopoietin, thrombopoietin receptor agonists, and platelet transfusion, will play a promising role in the treatment of the various liver disorders that currently challenge the surgical field.

Takahashi K, Murata S, Ohkohchi N. Platelet therapy: A novel strategy for liver regeneration, anti-fibrosis, and anti-apoptosis. *World J Surg Proced* 2013; 3(3): 29-36 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/29.htm DOI: http:// dx.doi.org/10.5412/wjsp.v3.i3.29

INTRODUCTION

Platelets contain bio-physiological substances, such as



Kazuhiro Takahashi, Soichiro Murata, Nobuhiro Ohkohchi, Department of Surgery, Division of Gastroenterological and Hepatobiliary Surgery and Organ Transplantation, University of Tsukuba, Ibaraki 305-8575, Japan

Author contributions: Takahashi K, Murata S and Ohkohchi N contributed equally to this work; Takahashi K wrote the paper. Correspondence to: Nobuhiro Ohkohchi, MD, PhD, Professor, Department of Surgery, Division of Gastroenterological and Hepatobiliary Surgery and Organ Transplantation, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575,

growth factors and cytokines^[1,2]. Platelets are activated by various types of stimulation, and they release these physiologically active substances in a context-dependent manner^[3]. The predominant function of platelets is in hemostasis and thrombosis, where they play a complex role with other cellular participants^[2,4]. Recently, platelets have been determined to have various roles in the body in addition to these primary functions^[5-7]. Plateletrich plasma is a source of platelet growth factors and cytokines^[8] and has increased in popularity since the late 1990s^[9]. Currently, platelet-rich plasma is widely accepted as the best treatment to promote would healing and tissue regeneration in many fields, including orthopedics^[10,11], plastic surgery^[12,13], and maxillofacial surgery^[14].

Thrombocytopenia is frequently observed in patients with chronic liver disease^[15]. This condition results from hypersplenism secondary to portal hypertension and decreased thrombopoietin production by hepatocytes^[16]. Liver regeneration after hepatectomy in this patient population is severely impaired, and preventing postoperative liver failure has long been considered a critical issue in the surgical fields^[17,18]. Recently, several attempts have been made to overcome this problem, including gene therapy^[19], bone marrow cell infusion therapy^[20], macrophage therapy^[21], and platelet therapy. In platelet therapy, thrombopoietin treatment and platelet transfusions have positive effects on the liver and are innovative treatments for various pathological liver conditions^[22,23]. Eltrombopag, an oral thrombopoietin agonist, has recently been developed^[24] and is beginning to be utilized to treat various health conditions, including liver disease^[25,26].

In this review, we present the experimental and clinical evidence that platelets accelerate liver regeneration and inhibit fibrosis and apoptosis; we also present the mechanisms of action for these functions. We propose that platelet therapy, including thrombopoietin and eltrombopag treatment and platelet transfusion, has a promising role in the treatment of the various liver problems, such as liver failure after a massive hepatectomy^[27], hepatectomy of a cirrhotic liver^[18], and small grafts in liver transplantation^[28], that currently challenge the surgical field.

PLATELETS AND LIVER REGENERATION

Liver regeneration after a hepatectomy is accomplished *via* the proliferation of hepatocytes, biliary epithelial cells, liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells^[29-31]. Intercellular interactions between numerous growth factors and cytokines, including hepatocyte growth factor (HGF), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), transforming growth factor- α , and endothelial growth factor, play important roles during this process^[29,30]. Each mediator activates downstream cascades by releasing hepatocytes from a quiescent state and allowing them to enter the cell cycle^[29,30]. The TNF- α /nuclear factor-kappa B (NF- κ B)^[32,33], IL-6/signal transducer and activator of transformation.

scription 3 (STAT3)^[34], and phosphatidylinositol-3-kinase (PI3K)/Akt^[35] pathways are the three major signaling cascades that are engaged during liver regeneration.

In 2004, Murata *et al*^[36] were the first to demonstrate that platelets promoted liver regeneration during the early phases after a partial hepatectomy. Using mouse models, Lesurtel *et al*^[37] reported that platelet-derived serotonin mediated liver regeneration. In this section, the clinical and experimental evidence that platelets promote liver regeneration and the three different mechanisms involved in this process are described.

Clinical evidence

In a retrospective analysis of 216 consecutive patients who underwent a partial hepatectomy for colorectal metastasis, Alkozai *et al*³⁸ reported that an immediate post-operative platelet count below $100000/\mu$ L was an independent risk factor for the delayed recovery of postoperative liver function and was associated with an increased risk of postoperative mortality. Kim *et al*³⁹ analyzed 87 patients who received adult-to-adult living donor liver transplants and determined that the total number of units of transfused platelet concentrate was significantly associated with graft regeneration, which was assessed by CT scan. Furthermore, the stepwise regression analysis revealed that the total amount of the platelets was independently associated with graft regeneration.

Effect of thrombocytosis on liver regeneration

Murata *et al*^[22] determined that a 2- to 3-fold elevation in platelet count induced by thrombopoietin increased the liver/body weight ratio, the hepatocyte Ki-67 labeling index, and the mitotic index after a 70% partial hepatectomy. Myronovych et $al^{[40]}$ reported that the incremental increase in platelet count after thrombopoietin treatment accelerated liver regeneration within 24 h after a 90% hepatectomy and improved the postoperative survival rate. They determined that under thrombocytotic conditions, there was a significant increase in HGF expression in liver tissue and the early phosphorylation of Akt and STAT3. These results implied that the thrombocytotic state induced by thrombopoietin promoted liver regeneration via an early activation of the PI3K/Akt and IL-6/ STAT3 pathways, leading to hepatocyte cell cycle entry and mitosis. In both studies, thromboembolic events, organ damage, and other side effects were not observed in response to the increased platelet count.

Effect of platelet transfusion on liver regeneration

Matsuo *et al*²³ examined the effects of platelet transfusion on liver regeneration by transfusing platelet-rich plasma into rats after a 70% partial hepatectomy. After a hepatectomy, platelet transfusion increased the liver/body weight ratio and the hepatocyte Ki-67 labeling index at 24 h without damaging the liver. Furthermore, platelet transfusion accelerated Akt phosphorylation and prolonged the activation of the extracellular signal-reg-





Figure 1 Platelet-mediated liver regeneration. Platelets accumulate in the liver immediately after a hepatectomy. A: Platelets translocate into the space of Disse and release insulin-like growth factor (IGF)-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) by directly contacting hepatocytes; B: Direct contact of platelets with liver sinusoidal endothelial cells induces the release of S1P from platelets and the secretion of interleukin-6 (IL-6) from liver sinusoidal endothelial cells: C: Kupffer cells activated in response to a hepatectomy induce the accumulation and activation of platelets. Growth factors released from platelets and the enhanced release of tumor necrosis factor- α (TNF- α) and IL-6 from Kupffer cells promote liver regeneration.

ulated kinase 1/2 pathway. These results indicated that platelet transfusion had a positive impact by accelerating liver regeneration after a hepatectomy without damaging the liver.

Mechanisms: The direct effect of platelets

Murata *et al*^{22]} observed that platelets accumulated in the liver immediately after a hepatectomy and translocated into the space of Disse to directly contact the hepatocytes. These data implied that platelets in the liver provide signals for hepatocyte proliferation through direct contact with hepatocytes. To prove this hypothesis, Matsuo *et al*^{41]} utilized a co-culture chamber system that separates the platelets and hepatocytes with a permeable membrane and clarified that direct contact between platelets and hepatocytes triggered the release of HGF, insulin-like growth factor (IGF)-1, and vascular endothelial growth factor (VEGF) from platelets, resulting in hepatocyte proliferation.

The direct effect of the platelet mechanism occurs when platelets translocate to the space of Disse and directly contact the hepatocytes, which triggers the secretion of HGF, IGF-1, and VEGF from the platelets. These growth factors initiate mitosis in hepatocytes and promote liver regeneration (Figure 1A).

Mechanism: The effect involving liver sinusoidal endothelial cells

Kawasaki *et al*^[42] studied the role of platelets in liver regeneration in relation to liver sinusoidal endothelial cells using co-culture chamber systems. They demonstrated that the direct contact of platelets with liver sinusoidal endothelial cells increased the release of IL-6 from liver sinusoidal endothelial cells, which accelerated DNA synthesis through the IL-6/STAT3 pathway in hepatocytes. They also proved that platelet-derived sphingosine-1-phosphate (S1P) induced IL-6 secretion from liver sinusoidal endothelial cells.

In the platelet mechanism of action that involves liver sinusoidal endothelial cells, the direct contact between the platelets and the liver sinusoidal endothelial cells induces S1P release from the platelets, which promotes IL-6 secretion from the liver sinusoidal endothelial cells. IL-6 subsequently accelerates hepatocyte mitosis *via* the IL-6/STAT3 pathway (Figure 1B).

Mechanism: The effect of Kupffer cells

Takahashi *et al*^[43] studied the positive impact of platelets on liver regeneration and focused on the role of Kupffer cells by transfusing platelets into mice. These authors discovered that after a 70% hepatectomy, transfused platelets accumulated and acted locally in the residual liver in the presence of activated Kupffer cells. The hepatic expression of TNF- α and IL-6, which are predominantly produced by Kupffer cells^[30,44], increased in response to a platelet transfusion, indicating that the function of the Kupffer cells was enhanced by a platelet transfusion. Furthermore, it was determined by electron microscopy that the transfused platelets were attached to the surface of the Kupffer cells, providing a reason why the platelets accumulated and were activated in the liver after a hepatectomy.

The mechanism involving platelets and Kupffer cells occurs when platelets accumulate and are locally activated in the liver by attaching to the surface of activated Kupffer cells. Liver regeneration is promoted by growth factors that are released from accumulated platelets and by the enhanced release of TNF- α and IL-6 from Kupffer cells (Figure 1C).

ANTI-FIBROSIS EFFECT OF PLATELETS

Liver fibrosis is a major cause of morbidity and mortality in the world^[45]. It results in liver failure, portal hy-



pertension, and an increased risk of carcinogenesis^[45,46]; liver transplantation is currently the only cure^[47]. Fibrosis is characterized by an excessive deposition of extracellular matrix proteins, which disrupt the liver structure and cause pathophysiological damage to this organ^[45,46]. Matrix metallopeptidases (MMPs) are enzymes that are responsible for the degradation of extracellular matrix proteins^[48,49], and the production of MMPs is regulated by HGF^[50,51]. Activated hepatic stellate cells are the primary cells that are responsible for the excessive synthesis of extracellular matrix proteins^[47]. Transforming growth factor- β (TGF- β), which is predominately released from hepatic stellate cells and Kupffer cells^[52], is the most potent cytokine that activates hepatic stellate cells. The effects of TGF- β are mediated by intracellular signaling *via* Smad proteins^[53], and TGF- β is suppressed by HGF^[19].

Despite improvements in the preoperative assessment of liver function and advances in surgical techniques, liver resection still carries the risk for postoperative hepatic failure, especially in patients with cirrhosis^[54]. This risk occurs because a cirrhotic liver has an impaired regenerative ability, and the risk of post-operative hepatic failure correlates with the degree of fibrosis^[55]. Accelerating liver regeneration and improving liver fibrosis would avoid liver failure after a hepatectomy. Although previous studies have viewed platelets as promoters of liver fibrosis^[56], recent studies have uncovered antifibrotic effects of platelets in the liver. This section describes the experimental and clinical evidence that platelets are anti-fibrotic as well as the mechanisms of action.

Clinical evidence

Maruyama et al^[57] conducted a prospective clinical trial of the effect of platelet transfusion on liver fibrosis. Patients with chronic liver disease (Child-Pugh classes A and B) and a platelet count below $100000/\mu$ L were registered. Ten patients received ten units of platelet concentrate once 1 wk for 12 wk. Four patients discontinued this treatment because of the appearance of mild hives, anti-human platelet antigen, and anti-human leukocyte antigen. Six patients completed the platelet transfusions and were followed for 9 mo after the last treatment; these patients exhibited increased concentrations of serum albumin and cholinesterase. Furthermore, there was a decrease in the serum hyaluronic acid, one of the serum fibrotic markers. It was determined that platelet transfusion improved liver function and decreased liver fibrosis.

Effect of thrombocytosis on liver fibrosis

Watanabe *et al*^{58]} reported that thrombocytosis induced by thrombopoietin treatment or splenectomy reduced liver fibrosis and the hydroxyproline content of liver tissue. Thrombocytosis suppressed TGF- β mRNA expression and increased MMP-9 expression in the liver. Furthermore, the liver volume, the hepatocyte proliferating cell nuclear antigen (PCNA) labeling index, and the mitotic index in fibrotic liver increased under thrombocytotic conditions. These findings indicated that thrombocytosis reduced liver fibrosis and promoted liver regeneration.

Murata *et al*^[59] examined the effect of a single thrombopoietin treatment on fibrosis and liver regeneration in a cirrhotic liver after a 70% partial hepatectomy. Thrombocytosis improved fibrosis and increased the hepatocyte PCNA labeling index and the mitotic index in the cirrhotic liver. The authors also injected anti-platelet serum after administering thrombopoietin to determine whether the effects were due to the thrombopoietin or to the increased platelet number. The anti-platelet serum injection significantly increased liver fibrosis and decreased liver regeneration. According to these studies, increasing the number of platelets attenuated liver fibrosis and accelerated liver regeneration even in a cirrhotic liver.

Mechanism: The direct effect of platelets

Ikeda et al^{60]} reported that platelet extracts suppressed hepatic stellate cell activation in vitro. They determined that adenine nucleotides, such adenosine triphosphate and adenosine diphosphate, were enriched in platelets and that ecto-nucleotide triphosphate diphosphodiesterase, ecto-nucleotide pyrophosphatase/phosphodiesterase, and ecto-5'-nucleotidase located on the plasma membrane of hepatic stellate cells degraded these adenine nucleotides to adenosine^[61]. The authors demonstrated that adenosine increased the intracellular concentration of cyclic adenosine 5'-monophosphate (cAMP) in hepatic stellate cells, which suppressed hepatic stellate cell activation by phosphorylating cAMP-response element binding protein. These findings indicated that hepatic stellate cell activation is directly suppressed by platelets via the adenosine-cAMP signaling pathway (Figure 2).

INHIBITION OF LIVER DAMAGE AND APOPTOSIS BY PLATELETS

Liver failure after a hepatectomy is caused by various events, including a massive hepatectomy, ischemic-reperfusion injury, and a postoperative infection^[62]. Hepatocyte apoptosis and diminished liver regeneration are the most important molecular events that occur during liver failure^[63]. Apoptosis is an active form of cell death, and two signaling pathways lead to apoptosis: the intrinsic and extrinsic pathways^[64]. The intrinsic pathway is characterized by mitochondrial dysfunction. Various stimuli damage the mitochondrial inner membrane, resulting in a permeability transition and the mitochondrial release of cytochrome C^[64]. In the cytosol, cytochrome C complexes with Apaf-1 to activate procaspase-9, which in turn activates its downstream effectors, caspases 3, 6, and 7, which are responsible for degrading several cellular substrates that are associated with the morphological changes representative of apoptosis^[65]. The Fas/Fas





Figure 2 Platelet-mediated inhibition of fibrosis. Platelets release adenosine nucleotides, which are degraded to adenosine by enzymes located on the plasma membrane of hepatic stellate cells. The activation of hepatic stellate cells is directly suppressed by the adenosine-cAMP signaling pathway.



Figure 3 Platelet-mediated inhibition of apoptosis. Platelets activate the Akt pathway and up-regulate Bcl-xL, which suppresses caspase-3 activation to prevent hepatocyte apoptosis.

ligand system plays an important role in the extrinsic pathway. Upon activation by the Fas ligand, Fas complexes with procaspase-8. The aggregation of this complex initiates the cleavage of procaspase-8 into its active form, which subsequently activates caspase-3, its downstream effector^[66]. Therefore, the Fas/Fas ligand system

affects both the intrinsic and extrinsic pathways. Bcl-xL, a member of the Bcl-2 family, prevents mitochondria permeability transition and Fas-mediated apoptosis by inhibiting the signaling cascades^[67].

This section describes the effect of thrombocytosis on liver damage and apoptosis. Because the Fas/Fas ligand system and apoptosis are hypothesized to be responsible for hepatitis^[68,69], we examined the anti-apoptotic effects using a hepatitis model.

Effect of platelets on liver damage and apoptosis after a massive hepatectomy

Hisakura *et al*⁷⁰ examined the ability of thrombopoietinmediated thrombocytosis to protect the liver from damage after an extended hepatectomy using a pig model. The authors discovered that in thrombocytotic conditions, liver cholestasis, ballooning, and necrosis were attenuated and that serum aspartate amino transferase and alkaline phosphatase (ALT) levels were low after an extended hepatectomy. Furthermore, electron transmission microscopy revealed that the structure of the endothelial lining was well preserved in thrombocytotic conditions. These data indicated that thrombocytosis protects the sinusoidal lining and prevents acute liver damage after an extended hepatectomy.

Hisakura *et al*^[71] also investigated the effects of throm-</sup>bocytosis in acute hepatitis induced by an anti-Fas antibody. The authors demonstrated that serum ALT levels were significantly decreased in thrombocytotic conditions at 6, 24 and 72 h after administering an anti-Fas antibody. They also determined that the percent of TdT-mediated dUTP-biotin nick end labeling-positive hepatocytes and the expression of cleaved caspase-3 in the liver were significantly decreased by thrombocytosis. Furthermore, in vitro Akt phosphorylation, increased Bcl-xL, and decreased cleaved caspase-3 were observed sequentially in hepatocytes co-cultured with platelets. Because Akt is a critical suppressor of apoptosis^[72,73], the above data suggested that an increase in the platelet count prevents hepatocyte apoptosis by activating the Akt pathway and upregulating Bcl-xL, which suppresses caspase-3 activation (Figure 3).

CONCLUSION

This review describes the published evidence that platelets promote liver regeneration, attenuate liver fibrosis, and prevent liver damage and hepatocyte apoptosis; it also details the mechanisms of action. In the blood, platelets are constituents that contain numerous biologically active growth factors and cytokines, and it was recently determined that platelets have various functions in addition to hemostasis and thrombosis^[5-7]. Currently, thrombopoietin^[22,40,58,59,70], thrombopoietin receptor agonists^[24], artificial platelets^[74,75], and freeze-dried platelets^[76] are in development and are beginning to be utilized in various clinical settings, and the importance of platelets is becoming more obvious. Despite some side effects^[57], platelet therapy has advantages in its convenience and cost-efficiency, and it provides another therapeutic strategy to address the current surgical issues and challenges, such as liver failure after a massive hepatectomy, hepatectomy of a cirrhotic liver, and small grafts in liver transplantation, in the near future.

REFERENCES

- Polasek J. Platelet secretory granules or secretory lysosomes? *Platelets* 2005; 16: 500-501 [PMID: 16287618]
- 2 Holmsen H. Physiological functions of platelets. *Ann Med* 1989; **21**: 23-30 [PMID: 2538134]
- 3 Blair P, Flaumenhaft R. Platelet α-granules: basic biology and clinical correlates. *Blood Rev* 2009; 23: 177-189 [PMID: 19450911 DOI: 10.1016/j.blre.2009.04.001]
- 4 Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev* 2011; 25: 155-167 [PMID: 21496978 DOI: 10.1016/ j.blre.2011.03.002]
- 5 Elzey BD, Sprague DL, Ratliff TL. The emerging role of platelets in adaptive immunity. *Cell Immunol* 2005; 238: 1-9 [PMID: 16442516 DOI: 10.1016/j.cellimm.2005.12.005]
- 6 Yamaguchi R, Terashima H, Yoneyama S, Tadano S, Ohkohchi N. Effects of platelet-rich plasma on intestinal anastomotic healing in rats: PRP concentration is a key factor. J Surg Res 2012; 173: 258-266 [PMID: 21074782 DOI: 10.1016/ j.jss.2010.10.001]
- 7 **Mehta P**. Potential role of platelets in the pathogenesis of tumor metastasis. *Blood* 1984; **63**: 55-63 [PMID: 6360248]
- 8 Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001; **10**: 225-228 [PMID: 11813662]
- 9 Rozman P, Bolta Z. Use of platelet growth factors in treating wounds and soft-tissue injuries. Acta Dermatovenerol Alp Panonica Adriat 2007; 16: 156-165 [PMID: 18204746]
- 10 Hartmann EK, Heintel T, Morrison RH, Weckbach A. Influence of platelet-rich plasma on the anterior fusion in spinal injuries: a qualitative and quantitative analysis using computer tomography. Arch Orthop Trauma Surg 2010; 130: 909-914 [PMID: 19949805 DOI: 10.1007/s00402-009-1015-5]
- 11 de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Tol JL. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA* 2010; 303: 144-149 [PMID: 20068208 DOI: 10.1001/jama.2009.1986]
- 12 Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and applications in plastic surgery. *Plast Reconstr Surg* 2006; **118**: 147e-159e [PMID: 17051095 DOI: 10.1097/01.prs.0000239606.92676.cf]
- 13 Redler LH, Thompson SA, Hsu SH, Ahmad CS, Levine WN. Platelet-rich plasma therapy: a systematic literature review and evidence for clinical use. *Phys Sportsmed* 2011; 39: 42-51 [PMID: 21378486 DOI: 10.3810/psm.2011.02.1861]
- 14 Dugrillon A, Eichler H, Kern S, Klüter H. Autologous concentrated platelet-rich plasma (cPRP) for local application in bone regeneration. *Int J Oral Maxillofac Surg* 2002; 31: 615-619 [PMID: 12521317 DOI: 10.1054/ijom.2002.0322]
- 15 Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Weksler B, Esteban R. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008; 48: 1000-1007 [PMID: 18433919 DOI: 10.1016/j.jhep.2008.03.009]
- 16 Rios R, Sangro B, Herrero I, Quiroga J, Prieto J. The role of thrombopoietin in the thrombocytopenia of patients with liver cirrhosis. *Am J Gastroenterol* 2005; **100**: 1311-1316 [PMID: 15929762]
- 17 McCormack L, Capitanich P, Quiñonez E. Liver surgery in the presence of cirrhosis or steatosis: Is morbidity increased? *Patient Saf Surg* 2008; **2**: 8 [PMID: 18439273 DOI:

10.1186/1754-9493-2-8]

- 18 Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; 30: 1434-1440 [PMID: 10573522 DOI: 10.1002/hep.510300629]
- 19 Ueki T, Kaneda Y, Tsutsui H, Nakanishi K, Sawa Y, Morishita R, Matsumoto K, Nakamura T, Takahashi H, Okamoto E, Fujimoto J. Hepatocyte growth factor gene therapy of liver cirrhosis in rats. *Nat Med* 1999; 5: 226-230 [PMID: 9930873 DOI: 10.1038/5593]
- 20 Terai S, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, Yokoyama Y, Uchida K, Yamasaki T, Fujii Y, Okita K, Sakaida I. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells* 2006; 24: 2292-2298 [PMID: 16778155]
- 21 Thomas JA, Pope C, Wojtacha D, Robson AJ, Gordon-Walker TT, Hartland S, Ramachandran P, Van Deemter M, Hume DA, Iredale JP, Forbes SJ. Macrophage therapy for murine liver fibrosis recruits host effector cells improving fibrosis, regeneration, and function. *Hepatology* 2011; 53: 2003-2015 [PMID: 21433043 DOI: 10.1002/hep.24315]
- 22 **Murata S**, Ohkohchi N, Matsuo R, Ikeda O, Myronovych A, Hoshi R. Platelets promote liver regeneration in early period after hepatectomy in mice. *World J Surg* 2007; **31**: 808-816 [PMID: 17354025 DOI: 10.1007/s00268-006-0772-3]
- 23 Matsuo R, Nakano Y, Ohkohchi N. Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. *Ann Surg* 2011; 253: 759-763 [PMID: 21475016 DOI: 10.1097/SLA.0b013e318211caf8]
- 24 Schipperus M, Fijnheer R. New therapeutic options for immune thrombocytopenia. *Neth J Med* 2011; 69: 480-485 [PMID: 22173361]
- 25 Boyers D, Jia X, Jenkinson D, Mowatt G. Eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a NICE single technology appraisal. *Pharmacoeconomics* 2012; **30**: 483-495 [PMID: 22480381]
- 26 Giannini EG, Afdhal NH. Eltrombopag in patients with chronic liver disease. *Expert Opin Pharmacother* 2013; 14: 669-678 [PMID: 23452139 DOI: 10.1517/14656566.2013.775249]
- 27 Garcea G, Maddern GJ. Liver failure after major hepatic resection. J Hepatobiliary Pancreat Surg 2009; 16: 145-155 [PMID: 19110651 DOI: 10.1007/s00534-008-0017-y]
- 28 Gruttadauria S, Pagano D, Luca A, Gridelli B. Small-forsize syndrome in adult-to-adult living-related liver transplantation. World J Gastroenterol 2010; 16: 5011-5015 [PMID: 20976835]
- 29 Fausto N. Liver regeneration. J Hepatol 2000; 32: 19-31 [PMID: 10728791]
- 30 Michalopoulos GK, DeFrances MC. Liver regeneration. *Science* 1997; **276**: 60-66 [PMID: 9082986]
- 31 Malik R, Selden C, Hodgson H. The role of non-parenchymal cells in liver growth. *Semin Cell Dev Biol* 2002; **13**: 425-431 [PMID: 12468243]
- 32 **Cressman DE**, Greenbaum LE, Haber BA, Taub R. Rapid activation of post-hepatectomy factor/nuclear factor kappa B in hepatocytes, a primary response in the regenerating liver. *J Biol Chem* 1994; **269**: 30429-30435 [PMID: 7982957]
- 33 FitzGerald MJ, Webber EM, Donovan JR, Fausto N. Rapid DNA binding by nuclear factor kappa B in hepatocytes at the start of liver regeneration. *Cell Growth Differ* 1995; 6: 417-427 [PMID: 7794809]
- 34 Cressman DE, Diamond RH, Taub R. Rapid activation of the Stat3 transcription complex in liver regeneration. *Hepa*tology 1995; 21: 1443-1449 [PMID: 7737651]
- 35 Jackson LN, Larson SD, Silva SR, Rychahou PG, Chen LA, Qiu S, Rajaraman S, Evers BM. PI3K/Akt activation is critical for early hepatic regeneration after partial hepatectomy. *Am J Physiol Gastrointest Liver Physiol* 2008; 294: G1401-G1410 [PMID: 18388186 DOI: 10.1152/ajpgi.00062.2008]
- 36 Murata S, Ohkohchi N, Abe T, Enomoto Y, Doi H, Satomi



S. Platelets promote G1-S progression of liver regeneration after hepatectomy. Bologna: MODIMOND S.r.l, 2004; E512C0241: 107-112

- 37 Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, Gachet C, Bader M, Clavien PA. Platelet-derived serotonin mediates liver regeneration. *Science* 2006; **312**: 104-107 [PMID: 16601191 DOI: 10.1126/science.1123842]
- 38 Alkozai EM, Nijsten MW, de Jong KP, de Boer MT, Peeters PM, Slooff MJ, Porte RJ, Lisman T. Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resection. *Ann Surg* 2010; 251: 300-306 [PMID: 19779326 DOI: 10.1097/SLA.0b013e3181b76557]
- 39 Kim J, Yi NJ, Shin WY, Kim T, Lee KU, Suh KS. Platelet transfusion can be related to liver regeneration after living donor liver transplantation. *World J Surg* 2010; 34: 1052-1058 [PMID: 20151125 DOI: 10.1007/s00268-010-0464-x]
- 40 Myronovych A, Murata S, Chiba M, Matsuo R, Ikeda O, Watanabe M, Hisakura K, Nakano Y, Kohno K, Kawasaki T, Hashimoto I, Shibasaki Y, Yasue H, Ohkohchi N. Role of platelets on liver regeneration after 90% hepatectomy in mice. *J Hepatol* 2008; 49: 363-372 [PMID: 18602717 DOI: 10.1016/j.jhep.2008.04.019]
- 41 Matsuo R, Ohkohchi N, Murata S, Ikeda O, Nakano Y, Watanabe M, Hisakura K, Myronovych A, Kubota T, Narimatsu H, Ozaki M. Platelets Strongly Induce Hepatocyte Proliferation with IGF-1 and HGF In Vitro. J Surg Res 2008; 145: 279-286 [PMID: 17688880 DOI: 10.1016/j.jss.2007.02.035]
- 42 Kawasaki T, Murata S, Takahashi K, Nozaki R, Ohshiro Y, Ikeda N, Pak S, Myronovych A, Hisakura K, Fukunaga K, Oda T, Sasaki R, Ohkohchi N. Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. *J Hepatol* 2010; **53**: 648-654 [PMID: 20615569 DOI: 10.1016/j.jhep.2010.04.021]
- 43 Takahashi K, Kozuma Y, Suzuki H, Tamura T, Maruyama T, Fukunaga K, Murata S, Ohkohchi N. Human platelets promote liver regeneration with Kupffer cells in SCID mice. *J Surg Res* 2013; 180: 62-72 [PMID: 23260232 DOI: 10.1016/j.jss.2012.11.030]
- 44 **Decker K**. The response of liver macrophages to inflammatory stimulation. *Keio J Med* 1998; **47**: 1-9 [PMID: 9560526]
- 45 Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005; 115: 209-218 [PMID: 15690074 DOI: 10.1172/JCI24282]
- 46 Friedman SL. Liver fibrosis--from bench to bedside. J Hepatol 2003; 38 Suppl 1: S38-S53 [PMID: 12591185]
- 47 Parsons CJ, Takashima M, Rippe RA. Molecular mechanisms of hepatic fibrogenesis. J Gastroenterol Hepatol 2007;
 22 Suppl 1: S79-S84 [PMID: 17567474 DOI: 10.1111/ j.1440-1746.2006.04659.x]
- 48 Hemmann S, Graf J, Roderfeld M, Roeb E. Expression of MMPs and TIMPs in liver fibrosis - a systematic review with special emphasis on anti-fibrotic strategies. *J Hepatol* 2007; 46: 955-975 [PMID: 17383048 DOI: 10.1016/j.jhep.2007.02.003]
- 49 Roderfeld M, Hemmann S, Roeb E. Mechanisms of fibrinolysis in chronic liver injury (with special emphasis on MMPs and TIMPs). Z Gastroenterol 2007; 45: 25-33 [PMID: 17236118 DOI: 10.1055/s-2006-927388]
- 50 Mizuno S, Matsumoto K, Li MY, Nakamura T. HGF reduces advancing lung fibrosis in mice: a potential role for MMP-dependent myofibroblast apoptosis. *FASEB J* 2005; 19: 580-582 [PMID: 15665032 DOI: 10.1096/fj.04-1535fje]
- 51 Higashiyama R, Inagaki Y, Hong YY, Kushida M, Nakao S, Niioka M, Watanabe T, Okano H, Matsuzaki Y, Shiota G, Okazaki I. Bone marrow-derived cells express matrix metal-loproteinases and contribute to regression of liver fibrosis in mice. *Hepatology* 2007; 45: 213-222 [PMID: 17187438]
- 52 Knittel T, Mehde M, Kobold D, Saile B, Dinter C, Ramadori G. Expression patterns of matrix metalloproteinases and their inhibitors in parenchymal and non-parenchymal cells of rat liver: regulation by TNF-α and TGF-β1. *J Hepatol* 1999; 30: 48-60 [PMID: 9927150]
- 53 Flanders KC. Smad3 as a mediator of the fibrotic response.

Int J Exp Pathol 2004; **85**: 47-64 [PMID: 15154911 DOI: 10.1111/j.0959-9673.2004.00377.x]

- 54 Takenaka K, Kanematsu T, Fukuzawa K, Sugimachi K. Can hepatic failure after surgery for hepatocellular carcinoma in cirrhotic patients be prevented? *World J Surg* 1990; 14: 123-127 [PMID: 2154902]
- 55 Nagasue N, Yukaya H, Ogawa Y, Kohno H, Nakamura T. Human liver regeneration after major hepatic resection. A study of normal liver and livers with chronic hepatitis and cirrhosis. *Ann Surg* 1987; 206: 30-39 [PMID: 3038039]
- 56 Zaldivar MM, Pauels K, von Hundelshausen P, Berres ML, Schmitz P, Bornemann J, Kowalska MA, Gassler N, Streetz KL, Weiskirchen R, Trautwein C, Weber C, Wasmuth HE. CXC chemokine ligand 4 (Cxcl4) is a platelet-derived mediator of experimental liver fibrosis. *Hepatology* 2010; 51: 1345-1353 [PMID: 20162727]
- 57 Maruyama T, Murata S, Takahashi K, Tamura T, Nozaki R, Ikeda N, Fukunaga K, Oda T, Sasaki R, Ohkohchi N. Platelet transfusion improves liver function in patients with chronic liver disease and cirrhosis. *Tohoku J Exp Med* 2013; 229: 213-220 [PMID: 23459612]
- 58 Watanabe M, Murata S, Hashimoto I, Nakano Y, Ikeda O, Aoyagi Y, Matsuo R, Fukunaga K, Yasue H, Ohkohchi N. Platelets contribute to the reduction of liver fibrosis in mice. *J Gastroenterol Hepatol* 2009; 24: 78-89 [PMID: 18624898 DOI: 10.1111/j.1440-1746.2008.05497.x]
- 59 Murata S, Hashimoto I, Nakano Y, Myronovych A, Watanabe M, Ohkohchi N. Single administration of thrombopoietin prevents progression of liver fibrosis and promotes liver regeneration after partial hepatectomy in cirrhotic rats. *Ann Surg* 2008; 248: 821-828 [PMID: 18948810 DOI: 10.1097/ SLA.0b013e31818584c7]
- 60 Ikeda N, Murata S, Maruyama T, Tamura T, Nozaki R, Kawasaki T, Fukunaga K, Oda T, Sasaki R, Homma M, Ohkohchi N. Platelet-derived adenosine 5'-triphosphate suppresses activation of human hepatic stellate cell: In vitro study. *Hepatol Res* 2012; 42: 91-102 [PMID: 21988364 DOI: 10.1111/j.1872-034X.2011.00893.x]
- 61 Dranoff JA, Ogawa M, Kruglov EA, Gaça MD, Sévigny J, Robson SC, Wells RG. Expression of P2Y nucleotide receptors and ectonucleotidases in quiescent and activated rat hepatic stellate cells. *Am J Physiol Gastrointest Liver Physiol* 2004; 287: G417-G424 [PMID: 14764443 DOI: 10.1152/ajpgi.00294.2003]
- 62 Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. *Dig Surg* 2012; 29: 79-85 [PMID: 22441624 DOI: 10.1159/000335741]
- 63 Yoshida N, Iwata H, Yamada T, Sekino T, Matsuo H, Shirahashi K, Miyahara T, Kiyama S, Takemura H. Improvement of the survival rate after rat massive hepatectomy due to the reduction of apoptosis by caspase inhibitor. *J Gastroenterol Hepatol* 2007; 22: 2015-2021 [PMID: 17559362 DOI: 10.1111/ j.1440-1746.2007.04960.x]
- 64 Malhi H, Gores GJ, Lemasters JJ. Apoptosis and necrosis in the liver: a tale of two deaths? *Hepatology* 2006; **43**: S31-S44 [PMID: 16447272 DOI: 10.1002/hep.21062]
- 65 Guicciardi ME, Gores GJ. Apoptosis: a mechanism of acute and chronic liver injury. *Gut* 2005; 54: 1024-1033 [PMID: 15951554 DOI: 10.1136/gut.2004.053850]
- 66 Bai J, Odin JA. Apoptosis and the liver: relation to autoimmunity and related conditions. *Autoimmun Rev* 2003; 2: 36-42 [PMID: 12848974]
- 67 Medema JP, Scaffidi C, Krammer PH, Peter ME. Bcl-xL acts downstream of caspase-8 activation by the CD95 deathinducing signaling complex. *J Biol Chem* 1998; 273: 3388-3393 [PMID: 9452459]
- 68 Leifeld L, Nattermann J, Fielenbach M, Schmitz V, Sauerbruch T, Spengler U. Intrahepatic activation of caspases in human fulminant hepatic failure. *Liver Int* 2006; 26: 872-879 [PMID: 16911471]

Takahashi K et al. Platelet therapy

- 69 Mita A, Hashikura Y, Tagawa Y, Nakayama J, Kawakubo M, Miyagawa S. Expression of Fas ligand by hepatic macrophages in patients with fulminant hepatic failure. *Am J Gastroenterol* 2005; 100: 2551-2559 [PMID: 16279913]
- 70 Hisakura K, Murata S, Fukunaga K, Myronovych A, Tadano S, Kawasaki T, Kohno K, Ikeda O, Pak S, Ikeda N, Nakano Y, Matsuo R, Konno K, Kobayashi E, Saito T, Yasue H, Ohkohchi N. Platelets prevent acute liver damage after extended hepatectomy in pigs. J Hepatobiliary Pancreat Sci 2010; 17: 855-864 [PMID: 20734209 DOI: 10.1007/s00534-010-0276-2]
- 71 Hisakura K, Murata S, Takahashi K, Matsuo R, Pak S, Ikeda N, Kawasaki T, Kohno K, Myronovych A, Nakano Y, Ikeda O, Watanabe M, Ohkohchi N. Platelets prevent acute hepatitis induced by anti-fas antibody. J Gastroenterol Hepatol 2011; 26: 348-355 [PMID: 21261726]
- 72 **Datta SR**, Dudek H, Tao X, Masters S, Fu H, Gotoh Y, Greenberg ME. Akt phosphorylation of BAD couples survival

signals to the cell-intrinsic death machinery. *Cell* 1997; **91**: 231-241 [PMID: 9346240]

- 73 **Stiles BL**. PI-3-K and AKT: Onto the mitochondria. *Adv Drug Deliv Rev* 2009; **61**: 1276-1282 [PMID: 19720099 DOI: 10.1016/j.addr.2009.07.017]
- 74 Bode AP, Fischer TH. Lyophilized platelets: fifty years in the making. Artif Cells Blood Substit Immobil Biotechnol 2007; 35: 125-133 [PMID: 17364477 DOI: 10.1080/10731190600974962]
- 75 Okamura Y, Takeoka S, Eto K, Maekawa I, Fujie T, Maruyama H, Ikeda Y, Handa M. Development of fibrinogen gammachain peptide-coated, adenosine diphosphate-encapsulated liposomes as a synthetic platelet substitute. *J Thromb Haemost* 2009; 7: 470-477 [PMID: 19143920]
- 76 Hoshi R, Murata S, Matsuo R, Myronovych A, Hashimoto I, Ikeda H, Ohkohchi N. Freeze-dried platelets promote hepatocyte proliferation in mice. *Cryobiology* 2007; 55: 255-260 [PMID: 17936259]
 - P- Reviewers: Asahina K, Matsuda Y, Pan GD, Tsuchiya A S- Editor: Zhai HH L- Editor: A E- Editor: Liu XM







Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.5412/wjsp.v3.i3.37 World J Surg Proced 2013 November 28; 3(3): 37-40 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

BRIEF ARTICLE

Treatment of cervico-mediastinal goiters

Prospero Magistrelli, Luigi D'Ambra, Pierfrancesco Bonfante, Elisa Francone, Rossella Leoncini, Mario Cappagli, Emilio Falco

Prospero Magistrelli, Luigi D'Ambra, Pierfrancesco Bonfante, Elisa Francone, Emilio Falco, Department of Surgery, S. Andrea Hospital, 19100, La Spezia, Italy

Rossella Leoncini, Mario Cappagli, Department of Nuclear Medicine, S. Andrea Hospital, 19100 La Spezia, Italy

Author contributions: All the authors made substantial contributions to the concept, design, acquisition and interpretation of data, reading and approving the final version of the manuscript. Correspondence to: Luigi D'Ambra, MD, Department of Sur-

gery, S. Andrea Hospital, Via Vittorio Veneto 197, 19100 La Spezia, Italy. luigidambra68@libero.it

 Telephone:
 +39-18-7533257
 Fax:
 +39-18-7533465

 Received:
 May 8, 2013
 Revised:
 September 3, 2013

Accepted: November 1, 2013

Published online: November 28, 2013

Abstract

AIM: To compare our ten year results for thyroidectomy for cervico-mediastinal goiters with the best surgical treatment reported in the literature.

METHODS: From January 2000 to December 2009, of 1530 patients who underwent thyroidectomy in our department, we selected 105 cases of cervico-mediastinal goiter. In the majority of cases, the cervical approach is the standard procedure and only occasionally sternotomy or thoracotomy is necessary. The indications for surgery are generally related to a progressive increase of the thyroid mass into the anterior mediastinum with compression and dislocation of the trachea or esophagus and the possibility of an unknown malignancy.

RESULTS: In 98 (93.3%) of our 105 patients, the standard surgical approach was anterior cervicotomy followed by total thyroidectomy. In three cases, total sternotomy was performed and in the remaining four patients, a partial split sternotomy was effective to remove the intrathoracic mass. Post-operative complications included transient recurrent laryngeal nerve palsy

in 6 patients (5.7%) which only became permanent in 2 patients (1.9%). The transient hypoparathyroidism rate was 22% but 2 mo after surgery permanent hypoparathyroidism was confirmed in only 2% of our selected group. No patients required temporary tracheostomy following surgery related to a possible bilateral nerve palsy. Patients received a single prophylactic antibiotic dose preoperatively and wound infections were not significant. There was no mortality in our selected group and most patients showed a significant improvement of dyspnea and other correlated symptoms postoperatively.

CONCLUSION: The majority of cervico mediastinal goiters can be completely removed through a cervical incision. In selected cases, generally malignancies with local infiltration of mediastinal soft tissues and adhesions to large vessels, split sternotomy may be a safer approach to not increase morbidity.

 $\ensuremath{\mathbb{C}}$ 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Goiter; Sternotomy; Thyroidectomy; Mediastinum; Thoracotomy

Core tip: The majority of cervico-mediastinal goiters can be completely removed through a cervical incision. Volume reduction by a vascular peduncle ligature can facilitate the extraction of big goiters, with the result that sternotomy or thoracotomy is seldom necessary. Care must be taken to avoid recurrent laryngeal nerve injuries.

Magistrelli P, D'Ambra L, Bonfante P, Francone E, Leoncini R, Cappagli M, Falco E. Treatment of cervico-mediastinal goiters. *World J Surg Proced* 2013; 3(3): 37-40 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/37.htm DOI: http:// dx.doi.org/10.5412/wjsp.v3.i3.37

90 WJSP | www.wjgnet.com

INTRODUCTION

Cervico-mediastinal goiters are a common pathology and their incidence may reach 15% of patients undergoing thyroidectomy^[1]. There is agreement that in the majority of cases, cervical approach is the standard procedure and only occasionally sternotomy or thoracotomy is necessary^[2]. The indications for surgery are generally related to a progressive increase of the thyroid mass into the anterior mediastinum with compression and dislocation of the trachea or esophagus and the possibility of an unknown malignancy.

In the past, medical treatment based on thyroxine was considered the first option to reduce the size of the gland. Now, surgery is also considered an appropriate treatment as negative intrathoracic pressure and retrosternal space tend to facilitate the migration of the goiter into the chest^[3]. We retrospectively reviewed our ten year experience to evaluate the choice of surgical approach, notes of surgical technique and range of complications with the aim to compare our results with the best surgical treatment reported in the literature.

MATERIALS AND METHODS

Cervico-mediastinal goiter is defined as a thyroid mass extending into the mediastinum in the prevascular or retrovascular space, reaching at least the level of the aortic arch. Surgical therapy considers extrathoracic enucleation of the thyroid mass. In this study, we excluded multinodular goiters with minimal or limited substernal extension.

From January 2000 to December 2009, of 1530 cases who underwent thyroidectomy in our department, we selected 105 patients operated on for cervico-mediastinal goiter. A total of 71 patients were women and 34 men, with a mean age of 61 years (range 22-80). All patients were referred to our unit by specialists and preoperative work up included blood examination and functional thyroid tests, chest X ray and a computed tomography (CT) scan to evaluate intrathoracic extension of the goiter. Only 23 of 105 patients underwent fine needle aspiration because of suspected nodules. The most frequent clinical symptoms are indicated in Table 1. Predominantly, patients reported a history of mild or severe dyspnea, although a considerable proportion (12 patients, 11.4%) had no palpable mass in the neck. In 5 cases (4.7%), the compression and dislocation of the trachea was masked by other conditions such as obstructive chronic diseases and asthma.

RESULTS

In 98 (93.3%) of our 105 patients, the standard surgical approach was anterior cervicotomy followed by total thyroidectomy. In three cases, total sternotomy was performed and in the remaining four patients, a partial split sternotomy was effective in removing the intrathoracic mass.

The combined approach was performed in the five

Table 1 Clinical symptoms n (%)

Symptoms	No. of patients	
Dyspnea	75 (71)	
Dysphagia	17 (16)	
Neck mass	86 (82)	
Hoarseness	14 (13)	

Table 2 Definitive histology				
Histology	n (%)			
Benign multinodular disease	86 (8.2)			
Papillary carcinoma	12 (11.5)			
Follicular carcinoma	5 (4.8)			
Medullary carcinoma	2 (1.9)			

cases of malignancy (3 papillary and 2 medullary carcinoma) and in two patients in which the inveterate multinodular goiters had established important adhesions with the mediastinal surrounding soft tissues.

Over the last five years, consolidation of our experience has avoided performing sternotomy even in cases of cervico-mediastinal goiters with development in the retrovascular space. The vast majority of patients were discharged in the second post-operative day. Two patients needed a re-exploration for wound hematoma and another three required further checks of blood calcium level.

Post-operative complications included transient recurrent laryngeal nerve palsy in 6 patients (5.7%) which only became permanent in 2 patients (1.9%). The transient hypoparathyroidism rate was 22% but 2 mo after surgery permanent hypoparathyroidism was confirmed in only 2% of our selected group. No patients required temporary tracheostomy following surgery related to a possible bilateral nerve palsy. Patients received a single prophylactic antibiotic dose preoperatively and wound infections were not significant. Definitive histology of the specimens is indicated in Table 2.

There was no mortality in our selected group and most patients showed a significant improvement of dyspnea and other correlated symptoms postoperatively.

DISCUSSION

Our selected group of patients was composed of cases with a prevalent anterior development of the cervical mass (Figure 1) and cases with dominant extension into the anterior mediastinum (Figure 2A). Development in the retrosternal space is favored by negative intrathoracic pressure and by gravity mechanisms. At first examination, the chest X-ray indicates the right or left dislocation of the trachea and this radiological evidence requires a CT scan for further definition of intrathoracic goiter (Figure 2).

In case of difficult oral intubation, evaluated preoperatively by the anesthesiologist, a fiber optic bronchoscopy guide was considered to facilitate the procedure.

The standard surgical approach to perform total





Figure 1 Giant multinodular goiter.



Figure 2 Computed tomography scan showing a mediastinal goiter descending between trachea and aortic arch (A) and surrounding trachea (B).

thyroidectomy was cervicotomy. Sternotomy has to be considered a selective option in cases of malignancy with soft tissue infiltration and/or gross mediastinal masses and lymphadenopathies which require a more aggressive surgery^[4,5]. We needed to execute total sternotomy only in the past decade. Nowadays, we perform split sternotomy in cases of invasive malignancy to avoid hemorrhage originating from mediastinal vessel laceration and malignant tumor relapses. Other factors that can influence the likelihood of sternotomy are posterior mediastinal and ectopic goiters. In these cases, gentle handle maneuvres do not permit a sufficient traction for enucleation^[6]. A mediastinal CT scan may be an important predictive factor. The presence of a clear plane around the intrathoracic nodule may be an indicator for a successful cervical



Figure 3 Post operative field showing inferior laryngeal nerve sparing.

approach^[1].

Our surgical strategy is based on two principles: (1) the section of superior thyroid peduncles and (2) clear evidence of recurrent laryngeal nerve course.

As a priority, we section superior vascular pedicles to reduce thyroid vascularization and consequently volume and tension of the gland. The further step is cervical enucleation of the mediastinal mass by using careful hand maneuvres.

Once the goiter is reduced, it is necessary to identify recurrent laryngeal nerves and following their course up to the larynx to avoid possible damage to a dislocated or compressive nerve caused by the thyroid mass (Figure 3). We do not section any structure until there is clear identification of the nerves and we emphasize this procedure because the recurrent laryngeal branches may reach the larynx with extreme variability through the tracheoesophageal groove.

Recently, a new technique based on nerve monitoring during surgery has been considered a good option that reduces but does not eliminate the risk of laryngeal nerve palsy. This electromyography, which is becoming a standard procedure in the United States, is becoming accepted in Europe, especially for legal medical reasons^[7].

At the moment, we are only considering nerve monitoring technique in cases of large relapsing goiters and this is because we systematically identify the nerves before any tissue section. However, the reported risk of nerve palsy using the monitoring technique is still around $1\%^{[7]}$. It must be emphasized that the complications of thyroid surgery need to be avoided for the important functional impact on the life quality of patients. There is agreement that this type of surgery needs to be performed by dedicated specialist surgeons. The majority of cervico-mediastinal goiters can be completely removed through a cervical incision.

In very selected cases, generally for malignancies with local infiltration of mediastinal soft tissues and adhesions to large vessels, split sternotomy may be a safer approach without increasing morbidity. Regular and systematic bilateral identification of recurrent laryngeal nerves and their variations is a priority to avoid complications. Our results are similar to the experiences reported by several Magistrelli P et al. A ten year single-institution experience

specialized center series.

COMMENTS

Background

The cervico-mediastinal goiter rate is about 15% of patients who undergoing thyroidectomy. Common agreement exists that in the majority of cases, the surgical cervical approach is the standard procedure and only occasionally sternotomy or thoracotomy is necessary. The indications for surgery are generally related to a progressive increase of the thyroid mass into the anterior mediastinum with compression and dislocation of the trachea or esophagus and the possibility of an unknown malignancy. In very selected cases, generally malignancies with local infiltration of mediastinal soft tissues and adhesions to large vessels, split sternotomy may be a safer approach without increasing morbidity.

Research frontiers

The standard surgical approach to perform total thyroidectomy is cervicotomy. Sternotomy has to be considered a selective option in case of cervico-mediastinal goiters and malignancy with soft tissue infiltration and/or gross mediastinal masses and lymphadenopathies which require a more aggressive surgery. The majority of cervico-mediastinal goiters can be completely removed through a cervical incision.

Innovations and breakthroughs

During thyroidectomy, identification of recurrent laryngeal nerves is mandatory to avoid possible injuries. Lately, a new technique based on nerve monitoring during surgery has been considered a valid option. In the authors' experience, a nerve monitoring technique is used only in cases of large relapsing goiters because the nerves are usually identified before any tissue section. However, the reported risk of nerve palsy using a monitoring technique is still around 1%.

Applications

The authors compare their ten year results in a surgical approach for thyroidectomy for cervico-mediastinal goiters with the best surgical treatment reported in the literature.

Peer review

The authors describe their experience of a cervicotomy approach for cervicomediastinal goiters, focusing on a nerve preserving technique and also highlighting the feasibility of the above-mentioned surgical procedure in a giant thyroid.

REFERENCES

- 1 **Cohen JP**. Substernal goiters and sternotomy. *Laryngoscope* 2009; **119**: 683-688 [PMID: 19160398 DOI: 10.1002/lary.20102]
- 2 Cichoń S, Anielski R, Konturek A, Baczyński M, Cichoń W, Orlicki P. Surgical management of mediastinal goiter: risk factors for sternotomy. *Langenbecks Arch Surg* 2008; 393: 751-757 [PMID: 18488246 DOI: 10.1007/s00423-008-0338-y]
- 3 Ahmed ME, Ahmed EO, Mahadi SI. Retrosternal goiter: the need for median sternotomy. *World J Surg* 2006; **30**: 1945-198; discussion 1949 [PMID: 16902739]
- 4 Ríos A, Rodríguez JM, Galindo PJ, Torres J, Canteras M, Balsalobre MD, Parrilla P. Results of surgical treatment in multinodular goiter with an intrathoracic component. *Surg Today* 2008; 38: 487-494 [PMID: 18516526 DOI: 10.1007/s00595-006-3673-z]
- 5 Ben Nun A, Soudack M, Best LA. Retrosternal thyroid goiter: 15 years experience. *Isr Med Assoc J* 2006; 8: 106-109 [PMID: 16544733]
- 6 Vadasz P, Kotsis L. Surgical aspects of 175 mediastinal goiters. Eur J Cardiothorac Surg 1998; 14: 393-397 [PMID: 9845144 DOI: 10.1016/S1010-7940(98)00204-8]
- 7 Chiang FY, Lee KW, Chen HC, Chen HY, Lu IC, Kuo WR, Hsieh MC, Wu CW. Standardization of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid operation. *World J Surg* 2010; 34: 223-229 [PMID: 20020124 DOI: 10.1007/s00268-009-0316-8]

P- Reviewer: Coskun A S- Editor: Zhai HH L- Editor: Roemmele A E- Editor: Zhang DN







Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.5412/wjsp.v3.i3.41 World J Surg Proced 2013 November 28; 3(3): 41-46 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

BRIEF ARTICLE

Operative indications of follicular type tumors, based on Japanese clinical guidelines

Hiroshi Takeyama, Isao Tabei, Kumiko Kato, Makio Kamio, Hiroko Nogi, Yasuo Toriumi, Satoki Kinoshita, Tadashi Akiba, Ken Uchida, Toshiaki Morikawa

Hiroshi Takeyama, Isao Tabei, Kumiko Kato, Makio Kamio, Hiroko Nogi, Yasuo Toriumi, Satoki Kinoshita, Tadashi Akiba, Ken Uchida, Toshiaki Morikawa, Department of Surgery, Jikei University School of Medicine, Tokyo 105-8461, Japan Author contributions: Takeyama H substantial contributed to conception, design, analysis and interpretation of data in this paper; Tabei I, Kato K, Kamio M, Nogi H and Toriumi Y contributed to acquisition of data; Kinoshita S, Akiba T and Uchida K contributed to revising it critically for important intellectual content; Morikawa T had final approval of the version to be published. Correspondence to: Hiroshi Takeyama, MD, Department of Surgery, Jikei University School of Medicine, 3-25-8, Nishishinbashi, Tokyo 105-8461, Japan. takeyama@jikei.ac.jp Telephone: +81-3-34331111-3401 Fax: +81-3-54724140 Received: May 16, 2013 Revised: July 10, 2013 Accepted: August 4, 2013 Published online: November 28, 2013

Abstract

AIM: To investigate the accuracy of preoperative examinations in follicular type tumors, we re-evaluate results of our operative cases.

METHODS: Cases are follicular neoplasms in 36 patients, which are more than 30 mm in diameter and underwent surgery in our hospital in 2005-2006. These cases had been suspected of malignancy on one or more of the preoperative examinations, including ultrasound (US), thallium-technecium (TI-Tc) scinitigram, computed tomography (CT), or fine needle aspiration biopsy (FNA) examinations. Concern about operative procedure, lobectomy plus sentinel lymph node biopsy (SNB) was performed in all 36 follicular tumors at the first surgery. Because we can diagnose a suspected follicular tumor as carcinoma and can change the operative procedure intra-operatively, when the metastasis of lymph nodes, outside of the thyroid, is found. The operative procedure was changed from lobectomy to total thyroidectomy plus lymph nodes dissection (central

component), when the SNB has metastasis. All thirty six cases were obtained to track the prognosis until 2012, for 6-7 years follow up periods.

RESULTS: The final pathological results are 3 cases of follicular carcinoma, 6 cases of papillary carcinoma, 1 case of papillary carcinoma follicular type, 1 case of malignant lymphoma, 16 cases of follicular adenoma, and 9 cases of adenomatous goiter. The malignant tumor were observed in 11/36 (30.6%) cases. All six papillary carcinomas were less than 20 mm, and present with follicular adenoma and adenomatous goiter, which have more than 40 mm diameter. In physical examination, tumor size of 36 cases of follicular neoplasm is more than 30 mm all at the time of surgery. The tumors were palpable somewhat stiff, such as no cystic component in 34 cases. Occasional dyspnea, dysphagia, and cough was accompanied in all 36 cases. The true ratio of correct diagnosis of preoperative US, TI-Tc scinitigram, CT, and FNA were 17/36 (47.2%), 16/36 (44.4%), 24/36 (66.7%), 21/36 (58.3%), respectively. In 11 malignant cases, there was one SNB positive case (one lymph node metastasis in 3 SNB: 1/3). This case was changed the operative procedure from lobectomy to total thyroidectomy plus lymph node dissection (central component). There is other lymph nodes metastasis in dissected lymph nodes (4/15). For the remaining malignant 10 cases, the observations were selected without additional resection, because surgical margins and SN were negative in postoperative pathology results at the first operation. No recurrence and metastasis are allowed in 11 malignant cases, up to 7 years after post-operation. Over all, the more than 30 mm in diameter follicular neoplasms, which were suspected the malignancy in the one and more preoperative examinations, are present the malignancy by pathological diagnosis in 11/36 (30.6%) cases after surgery. The non SNB metastasis cases had no symptoms of lymph nodes metastasis up to 7 years after post-operation.



Takeyama H et al. Operative indications of follicular type tumors

CONCLUSION: We think that more than 30 mm in diameter follicular neoplasms are considered as candidates of surgery from our results.

 \odot 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Follicular type tumor; Preoperative diagnosis; Operative indication; Guideline of thyroid tumor; Prognosis

Core tip: To know the accuracy of preoperative examinations, we investigated the operated 36 follicular type tumors, according to the postoperative final pathological diagnosis. We also re-evaluate the operative indication and operative procedure. The true ratio of correct diagnosis of preoperative ultrasound, thalliumtechnecium scinitigram, computed tomography, or fine needle aspiration biopsy were 17/36 (47.2%), 16/36 (44.4%), 24/36 (66.7%), 21/36 (58.3%), respectively, and there were no statically differences between the accuracy of these preoperative diagnoses. The more than 30 mm in diameter tumors, which were suspected the malignancy in the one and more preoperative examinations, are present the malignancy in 11/36 (30.6%) cases by final pathological diagnosis.

Takeyama H, Tabei I, Kato K, Kamio M, Nogi H, Toriumi Y, Kinoshita S, Akiba T, Uchida K, Morikawa T. Operative indications of follicular type tumors, based on Japanese clinical guidelines. *World J Surg Proced* 2013; 3(3): 41-46 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/41.htm DOI: http://dx.doi.org/10.5412/wjsp.v3.i3.41

INTRODUCTION

The diagnostic accuracy of papillary carcinoma is over 90% by preoperative examinations. On the other hand, the diagnostic accuracy of follicular type tumors is only 20%-40%.

For example, the accuracy of fine needle aspiration biopsy (FNA) is more than 90% in papillary carcinoma, because the morphology of papillary cell has some distinctive features, such as intra-nuclear inclusion or notching of nuclei. In contrast, there are no differences between follicular malignant tumors and benign follicular tumors morphologically by FNA. For the preoperative diagnosis of thyroid tumor, ultrasound (US) examination, thallium-technecium (TI-Tc) scinitigram, computed tomography (CT), and fine needle aspiration biopsy (FNA) are usually recommended. We decided the operative indication and resected area with these results.

Recently, some physical signs and radiological imagings are indicated as the detection tools of malignant follicular type tumor by the new Japanese guide line of thyroid tumor, published in 2010^[1]. In this study, we re-evaluate the results of preoperative examinations of follicular type tumors according to the guide line, using the pathologically final diagnosed cases, and re-consider the operative indications.

MATERIALS AND METHODS

Case and examinations

Cases are follicular neoplasms in 36 patients, which are more than 30 mm in diameter and underwent surgery in our hospital in 2005-2006. These cases had been suspected of malignancy by the one or more of preoperative examinations, including US, Tl-Tc scinitigram, CT, or FNA examinations.

Operative procedure

Usually, the operation of follicular type tumor performs tumor-side lobectomy, as the differential diagnosis is difficult in preoperative examinations.

In the Japanese thyroid cancer treatment protocol in 2005 Edition^[2], follicular carcinoma diagnostic criteria are determined as follows: (1) membrane invasion of the tumor cells; (2) lymphatic or vessel duct invasion of the tumor cell; and (3) metastasis outside of the thyroid gland being able to confirm one of either of these histological examinations.

In this study, we tried the lobectomy plus sentinel nodes biopsy (SNB) as a first operation. Because we can diagnose a follicular tumor as carcinoma and can change the operative procedure intra-operatively, when the metastasis of lymph nodes, outside of the thyroid, is found.

Pathological diagnosis

The final diagnosis of tumor was determined by formalin-fixed, Hematoxylin-Eosin (HE) stained specimen after surgery. SNB was evaluated by HE stained frozen section intra-operatively, and reevaluated by formalinfixed specimen after surgery.

RESULTS

The final pathological diagnosis

The final pathological diagnosis and the results of preoperative examinations were summarized in Tables 1 and 2. The pathological diagnoses are 3 cases of follicular carcinoma (diameter 40-54 mm), 6 cases of papillary carcinoma (5-14 mm), 1 case of papillary carcinoma follicular variant type (30 mm), 1 case of malignant lymphoma (45 mm), 16 cases of follicular adenoma (30-80 mm), 9 cases of adenomatous goiter (43-170 mm). The malignant tumors were observed in 11/36 (30.6%) cases.

About seven papillary carcinomas including follicular variant type, 6 papillary carcinomas were present with adenoma and adenomatous goiter that have more than 40 mm diameter (Figure 1).

In 36 patients performed SNB intraoperative, there was one positive metastasis case of papillary carcinoma follicular variant type (1/36, 2.7%).





Figure 1 Hematoxilin-Eosin staining shows micropapillary carcinoma (diameter 10 mm, arrow, upper part) with follicular adenoma (diameter 50 mm, lower part).



Figure 2 A tumor diameter of approximately 60 mm, solid and accounts for most of the left lobe were suggested by ultrasound. Although capsular invasion was unclear, Doppler examination were revealed abundant blood flow and high blood flow resistance value inside the tumor. The result of ultrasound suspected the malignancy.

Table 1Final pathological diagnosis of follicular type tumorthat was suspected malignancy by preoperative examinations

Pathological diagnosis	Cases	Tumor size (mm)
Malignant lesion		
Papillary carcinoma	7	5-30
Follicular carcinoma	3	40-54
Malignant lymphoma	1	45
Benign lesion		
Follicular adenoma	16	33-80
Adenomatous goiter	9	43-170

Examinations

Physical examination: Tumor size of 36 cases is more than 30 mm all at the time of surgery. The tumors were palpable somewhat stiff, such as no cystic component in 34 cases. Occasional dyspnea, dysphagia, and cough was accompanied in all 36 cases, but was not accompanied lymph node swelling, paralysis of the vocal cords.

US: US examination diagnosed 24 cases as benign tumors including adenoma, adenomatous goiter, and 12 cases as suspicion of malignant or malignant tumor. The





Figure 3 In the TI early phase of 5 min after injection, a prominent accumulation of isotope to the tumor was observed. In the delay phase of 120 min after injection, a remaining of isotope in tumor was also found. These accumulations of isotope and delay of wash out suggest the suspicion of malignancy findings.

true positive ratio (TP) was 2/11 (18.2%), the true negative ratio (TN) 15/25 (60.0%), the false-positive ratio (FP) 10/25 (40.0%), the false negative ratio (FN) 9/11 (81.8%), respectively. The true ratio (TR) of correct diagnosis (TP + TN/Total cases) by US was 17/36 (47.2%). The malignant tumor suspected by US, were indicated in Figure 2.

Scintigraphy (TI-Tc scinitigram): TI-Tc scinitigram examination diagnosed 9 cases as benign tumor, and 27 cases as suspicion of malignant or malignant tumor. TP was 9/11 (81.8%), TN7/25 (28.0%), FP18/25 (72.0%), FN 9/11 (81.8%), respectively. TR by TI-Tc scinitigram was 16/36 (44.4%). The malignant tumor suspected by scintigraphy was suggested in Figure 3.

CT: CT examination diagnosed 31 cases as benign tumor, and 5 cases as suspicion of malignant or malignant tumor (Figure 4).

TP was 2/11 (18.2%), TN 22/25 (88.0%), FP 3/25 (12.0%), FN 9/11 (81.8%), respectively. TR by CT was 24/36 (66.7%).

FNA: Twenty cases were benign, and 16 cases were suspicion of malignancy by FNA examination. TP was 6/11 (54.5%), TN 15/25 (60.0%), FP 10/25 (40.0%), and FN 5/11 (45.5%), respectively. TR by FNA was also 21/36 (58.3%).

Takeyama H et al. Operative indications of follicular type tumors



Figure 4 Computed tomography image of follicular neoplasm of 45 mm diameter in the right lobe. It showed some irregular border and extension of the right wall of the trachea. There is a suspicion of tracheal invasion of tumor.

Table 2True positive, true negative, and accuracy rates ofpreoperative examinations, based on the final pathologicaldiagnosis of follicular tumors

	us	TI-Tc scinitigram	СТ	FNA
True positive: TP (malignant)	2 (18.2)	9 (81.8)	2 (18.2)	6 (54.5)
True negative: TN (benign)	15 (40.0)	7 (28.0)	22 (88.0)	15 (60.0)
TP + TN (accuracy)	17 (47.2)	16 (44.2)	24 (66.7)	21 (58.3)

US: Ultrasound; TI-Tc: Thallium-technecium, scinitigram; CT: Computed tomography; FNA: Fine needle aspiration biopsy; TN: True negative ratio; TP: True positive ratio.

Operation: Lobectomy plus SNB was performed in all 36 follicular tumors at the first surgery.

Figure 5A is a statue of SN identification using Tcphysic acid for the 40 mm diameter follicular neoplasm of the right lobe.

Figure 5B is the photo of SN stained by the dye at the time of surgery of the same case. The stained SN was acknowledged in the central component lymph nodes near the right recurrent nerve. The SN was counted the accumulation of isotope, excised, and submitted to the intraoperative pathologic examination to confirm the presence or absence of lymph node metastasis. In 36 patients, there was one positive lymph nodes metastasis case (SNB: 1/3). The surgical procedure was changed to total thyroidectomy plus lymph node dissection (central component) during surgery in this case. There is other lymph nodes metastasis in dissected lymph nodes (4/15).

For the remaining malignant 10 cases, the observations were selected without additional resection, because surgical margins and SN were negative in postoperative pathological diagnosis.

Prognosis

The recurrence or metastasis has not been recognized in these 11 cases of malignant tumor from 2005 to 2012, more than five years after surgeries.



Figure 5 Sentinel nodes. A: Sentinel nodes (SNL, arrow) revealed in the central component lymph nodes using Tc-physic acid. B: SNL (arrow) is performed using 4% isosulfan blue dye during operation. The stained lymph node is seen near the right pharyngeal recurrent nerve in the central component lymph nodes.

DISCUSSION

In clinical question (CQ) 6 of the 2010 Thyroid Tumor Treatment Guidelines created by Japan Endocrine Surgery Society/Japan Thyroid Surgery Society, US, Tl-Tc scintigraphy, CT, and fluoro-deoxyglucose positron emission tomography are given as diagnostic imaging methods in the diagnosis of malignant tumors as grade B recommendations^[1,3-5]. Among these, US is recommended as the most useful modality^[1,6-8].

In this follicular tumor study, correct diagnostic rates of FNA and CT were relative high with 50%-60% on the preoperative examinations.

When we compared these 2 examinations, true positive rate, both true negative rates were more than 50% together in FNA examination. On the other hand, the CT test identified true positive rate 18.2%, and true negative rates 88.0%.

So, we think that FNA is a reliable examination for distinguish malignant and benign follicular tumor than CT study, although there is thought to be room for improvement, as many reports mentioned that diagnosis of follicular malignant neoplasm was more difficult than diagnosis of papillary carcinoma^[1,5-8].

CQ 5 of the guidelines state that "physical findings that increase the possibility of malignant neoplasm in thyroid tumors include adhesion to tissues surrounding



WJSP | www.wjgnet.com

nodes, lymph node enlargement, vocal cord paralysis (hoarseness), dyspnea, dysphagia, coughing" and "especially in tumor size alone, nodes of ≥ 40 mm are a significant independent factor suggestive of malignancy" ^[1,9-14]. In addition, when a tumor is follicular carcinoma, tumor size ≥ 40 mm become stage III in the tumor node metastasis classification of Union for International Cancer Control, and the chance of remote metastasis will be increased.

Surgery is thought to be indicated in that reason for the follicular tumors ≥ 40 mm, which can not deny the malignancy^[15,16].

In our results, only 3 of 28 follicular tumors ≥ 40 mm in diameter were follicular carcinoma (10.7%), and 5 of 36 follicular tumors ≥ 30 mm that were suspected the malignancy by several preoperative examinations, were malignant tumors (13.9%). Concerning about papillary carcinoma, although the size of papillary carcinoma were less than 20 mm, 6 cases coexisted with follicular adenoma and adenomatous goiter ≥ 40 mm that were benign on postoperative pathological diagnosis.

As described above, the malignancy rate of follicular tumors ≥ 40 mm was not high. However, considering coexisting lesions such as papillary carcinoma with benign follicular tumors ≥ 40 mm, the malignant region was present in a total of 12 of 36 suspected tumor (33.3%). So, we concluded that surgery is thought to be indicated as stated in the guidelines.

For SNB, such as follicular variant of papillary carcinoma that have a fairly high frequency of lymph node metastasis, the surgical procedure can be changed depending on lymph node metastasis status during surgery. So, SNB is thought to have a high likelihood of being useful^[15,17].

It is a tiny and one facility study, we think that follicular neoplasms ≥ 40 mm in diameter, which had been suspected of malignancy on one or more of the preoperative examination are considered as candidates of surgery, as suggested in the Treatment of Thyroid Tumor-Japanese Clinical Guidelines^[1].

COMMENTS

Background

The diagnostic accuracy of papillary carcinoma is over 90% by preoperative examinations. On the other hand, the diagnostic accuracy of follicular type tumors is only 20%-40%.

Research frontiers

Recently, some physical signs and radiological imagings are indicated as the detection tools of malignant follicular type tumor by the new Japanese guide line of thyroid tumor, published in 2010. In this study, they re-evaluate the results of preoperative examinations of follicular type tumors according to the guide line, using the pathologically final diagnosed cases, and re-consider the operative indications.

Innovations and breakthroughs

In their results, only 3 of 28 follicular tumors ≥ 40 mm in diameter were follicular carcinoma (10.7%), and 5 of 36 follicular tumors ≥ 30 mm that were suspected the malignancy by several preoperative examinations, were malignant tumors (13.9%). Concerning about papillary carcinoma, although the size of papillary carcinoma were less than 20 mm, 6 cases coexisted with follicular

adenoma and adenomatous goiter \geq 40 mm that were benign on postoperative pathological diagnosis. As described above, the malignancy rate of follicular tumors \geq 40 mm was not high. However, considering coexisting lesions such as papillary carcinoma with benign follicular tumors \geq 40 mm, the malignant region was present in a total of 12 of 36 suspected tumor (33.3%). So, the authors concluded that surgery is thought to be indicated as stated in the guide-lines.

Applications

Authors think that follicular neoplasms ≥ 40 mm in diameter, which had been suspected of malignancy on one or more of the preoperative examination are considered as candidates of surgery, as suggested in the Treatment of Thyroid Tumor-Japanese Clinical Guidelines.

Peer review

This is a very interested topic for the readers. It shows the guidelines of the Japanese Society of Endocrine Surgery.

REFERENCES

- 1 **Takami H**, Yoshida A, Okamoto T, editors. Treatment of Thyroid Tumor--Japanese Clinical Guidelines. Tokyo: KANEHARA Publishing, 2010: 33-39
- 2 Miyauchi A, Sakamoto A, Kakudo K, editors. General rules for description of thyroid cancer by the Japanese society of thyroid surgery. 6th ed. Tokyo: KANEHARA Publishing, 2006: 13-16
- 3 Ishigaki S, Shimamoto K, Satake H, Sawaki A, Itoh S, Ikeda M, Ishigaki T, Imai T. Multi-slice CT of thyroid nodules: comparison with ultrasonography. *Radiat Med* 2004; 22: 346-353 [PMID: 15553016]
- 4 Tamizu A, Okumura Y, Sato S, Takeda Y, Maki K, Hiraki T, Akaki S, Kuroda M, Kanazawa S, Hiraki Y. The usefulness of serum thyroglobulin levels and Tl-201 scintigraphy in differentiating between benign and malignant thyroid follicular lesions. *Ann Nucl Med* 2002; 16: 95-101 [PMID: 12043914]
- 5 de Geus-Oei LF, Pieters GF, Bonenkamp JJ, Mudde AH, Bleeker-Rovers CP, Corstens FH, Oyen WJ. 18F-FDG PET reduces unnecessary hemithyroidectomies for thyroid nodules with inconclusive cytologic results. J Nucl Med 2006; 47: 770-775 [PMID: 16644746]
- 6 Ota H, Ito Y, Matsuzuka F, Kuma S, Fukata S, Morita S, Kobayashi K, Nakamura Y, Kakudo K, Amino N, Miyauchi A. Usefulness of ultrasonography for diagnosis of malignant lymphoma of the thyroid. *Thyroid* 2006; 16: 983-987 [PMID: 17042683]
- 7 **Fish SA**, Langer JE, Mandel SJ. Sonographic imaging of thyroid nodules and cervical lymph nodes. *Endocrinol Metab Clin North Am* 2008; **37**: 401-417, ix [PMID: 18502334]
- 8 Kabaker AS, Tublin ME, Nikiforov YE, Armstrong MJ, Hodak SP, Stang MT, McCoy KL, Carty SE, Yip L. Suspicious ultrasound characteristics predict BRAF V600E-positive papillary thyroid carcinoma. *Thyroid* 2012; 22: 585-589 [PMID: 22524468 DOI: 10.1089/thy.2011.0274]
- 9 Atli M, Akgul M, Saryal M, Daglar G, Yasti AC, Kama NA. Thyroid incidentalomas: prediction of malignancy and management. *Int Surg* 2006; **91**: 237-244 [PMID: 16967687]
- 10 Mitchell JC, Grant F, Evenson AR, Parker JA, Hasselgren PO, Parangi S. Preoperative evaluation of thyroid nodules with 18FDG-PET/CT. *Surgery* 2005; 138: 1166-1174; discussion 1174-1175 [PMID: 16360405]
- 11 Lawrence W, Kaplan BJ. Diagnosis and management of patients with thyroid nodules. J Surg Oncol 2002; 80: 157-170 [PMID: 12115799]
- 12 Datta RV, Petrelli NJ, Ramzy J. Evaluation and management of incidentally discovered thyroid nodules. *Surg Oncol* 2006; 15: 33-42 [PMID: 16935490]
- 13 Chan WF, Lo CY, Lam KY, Wan KY. Recurrent laryngeal nerve palsy in well-differentiated thyroid carcinoma: clinicopathologic features and outcome study. *World J Surg* 2004; 28: 1093-1098 [PMID: 15490071]

Takeyama H et al. Operative indications of follicular type tumors

- 14 **Lansford CD**, Teknos TN. Evaluation of the thyroid nodule. *Cancer Control* 2006; **13**: 89-98 [PMID: 16735982]
- 15 Stang MT, Carty SE. Recent developments in predicting thyroid malignancy. *Curr Opin Oncol* 2009; 21: 11-17 [PMID: 19125013 DOI: 10.1097/CCO.0b013e32831db2af]
- 16 **McCaffrey TV**. Evaluation of the thyroid nodule. *Cancer Control* 2000; **7**: 223-228 [PMID: 10832108]
- 17 Takeyama H, Tabei I, Uchida K, Morikawa T. Sentinel node biopsy for follicular tumours of the thyroid gland. Br J Surg 2009; 96: 490-495 [PMID: 19358183 DOI: 10.1002/bjs.6559]

P- Reviewer: Rodriguez DC S- Editor: Gou SX L- Editor: A E- Editor: Liu XM







doi:10.5412/wjsp.v3.i3.47

Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com

World J Surg Proced 2013 November 28; 3(3): 47-53 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

META-ANALYSIS

Back to basics: A meta-analysis of stump management during open appendicectomy for uncomplicated acute appendicitis

Gianpiero Gravante, Shuker Yahia, Roberto Sorge, George Mathew, Ashish Kelkar

Gianpiero Gravante, Ashish Kelkar, Department of Colorectal Surgery, Kettering General Hospital, NN16 8UZ Kettering, United Kingdom

Shuker Yahia, George Mathew, Department of Colorectal Surgery, George Eliot Hospital, CV10 7DJ Nuneaton, United Kingdom Roberto Sorge, Department of Human Physiology, Laboratory of Biometry, University of Rome "Tor Vergata", 00173 Rome, Italy

Author contributions: Gravante G and Yahia S collected and analysed the data and wrote the article; Sorge R performed the statistical analysis on data, interpreted them and critically revised the article; Mathew G and Kelkar A contributed to conception and design of the article and critically revised it; all authors gave the approval to the final draft.

Correspondence to: Gianpiero Gravante, BSC, MBBS, PhD, Department of Colorectal Surgery, Kettering General Hospital, Rothwell Road 10, NN16 8UZ Kettering,

United Kindom. ggravante@hotmail.com

 Telephone: +44-116-168244
 Fax: +39-623-3216592

 Received: July 28, 2013
 Revised: September 2, 2013

 Accepted: September 14, 2013
 Published online: November 28, 2013

Abstract

AIM: To compare simple ligation *vs* stump invagination during open appendicectomy for uncomplicated acute appendicitis on the risk of postoperative complications.

METHODS: A meta-analysis was conducted on randomised controlled trials comparing the two stump closure methods in open appendicectomy. Databases searched were PubMed, EMBASE and Cochrane Library databases. Included were those studies focusing on inflamed and suppurative appendicitis while perforated and gangrenous appendix was excluded. We also excluded retrospective case-control studies, commentaries, historical technical articles, or trials involving laparoscopic appendicectomies. The outcome of the meta-analysis was to find eventual differences in the incidence of postoperative ileus and wound infections between the two techniques of stump invagination.

RESULTS: Seven studies were included corresponding to 1468 patients. Postoperative complications consisted in wound infections (7%), ileus (4%), pyrexia (2%), vomiting (1%), obstructions from adhesions (0.1%). No cases of peritonitis, fecal fistulas (stump leaks), abdominal abscesses or wound dehiscences were reported. Postoperative ileus within the first 72 h was four times more frequent with stump invagination compared to simple ligation (OR: 4.06; 95%CI: 2.14-7.70; P < 0.0001). No significant differences were noted for wound infections (OR: 1.24; 95%CI: 0.83-1.87; P = 0.30) while for the remaining complications the incidence was extremely low in both groups. There was a high homogeneity on results (Q value for heterogeneity of postoperative ileus P = 0.17; Q value for heterogeneity of wound infections P = 0.98).

CONCLUSION: Stump invagination does not seem to prevent infective complications but is associated with an increased risk of postoperative ileus in uncomplicated cases. Appropriate studies on complicated appendicitis should now evaluate the influence of the two techniques in this higher-risk subgroup.

 $\ensuremath{\mathbb{C}}$ 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Appendiceal stump; Open appendicectomy; Invagination; Appendicitis; Complications

Core tip: Despite the increased use of the laparoscopic approach, open appendicectomy is an operation still performed on a large scale worldwide. Two main approaches exist for the stump closure, the simple ligation and the stump invagination. Compared to the simple ligation the invagination of the stump aim to provide an extra safety measure for the prevention



of postoperative complications, but the study demonstrated that in cases of non-complicated appendicitis it increases the risks of postoperative ileus and does not decrease the wound infections rate.

Gravante G, Yahia S, Sorge R, Mathew G, Kelkar A. Back to basics: A meta-analysis of stump management during open appendicectomy for uncomplicated acute appendicitis. *World J Surg Proced* 2013; 3(3): 47-53 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/47.htm DOI: http://dx.doi.org/10.5412/wjsp.v3.i3.47

INTRODUCTION

In recent years the combined advantages of better diagnosis and reduced surgical trauma have progressively favoured the laparoscopic appendicectomy (LA) over open appendicectomy (OA) for the treatment of acute appendicitis. In numerous studies and meta-analyses LA has achieved less postoperative pain, reduced hospital stay and faster return to normal daily activities compared to OA at the cost of longer operating times^[1-3]. Despite these positive results OA is still frequently performed worldwide: 34% of appendicitis patients receive OA in the United Kingdom^[4], 45% (university teaching hospitals) to 75% (district general hospitals) in Ireland^[5], and more than 50% in Italy^[6,7]. Additionally, OA is still necessary when LA requires conversion to an open approach (i.e., dense adhesions, diffuse peritonitis, difficulties in excision of the appendix due to perforation)^[8], or in special circumstances such as pregnancy where the avoidance of the pneumoperitoneum and CO2 systemic absorption decrease the rate of fetal loss^[9].

One of the historical controversies of the open technique involves the management of the appendiceal stump following removal of the appendix. A long stump may produce recurrences (appendiceal stumpitis)^[10]. While an inadequate closure contaminates the abdominal cavity with fecal material (fecal fistula). In both cases, the postoperative outcome is endangered and re-operations with bowel resections may become necessary. Two approaches have been described over the years for the management of the appendiceal stump during OA. The first and simplest approach is the simple ligation (SL), described in 1884^[11,12]. The second consists in the ligation and invagination of the stump (SI) in the cecum^[11,12] by a purse-string suture or a Z-stitch^[13-18]. This was introduced to secure the stump in the bowel lumen so that any perforation or leakage would directly drain inside the gut and not in the abdominal cavity.

Both approaches have been compared in numerous trials for their ability to prevent postoperative infections, ileus and other complications but results from single studies have been contrasting. In the present article we decided to conduct a meta-analysis on those trials to evaluate the influence of SL and SI on the occurrence of postoperative complications following OA.

MATERIALS AND METHODS

The meta-analysis has been reported according to the QUORUM and MOOSE guidelines^[19,20].

Study selection and data extraction

Included articles were (1) randomized controlled trials (RCTs) that (2) focused on the technique for stump management during OA for (3) uncomplicated acute appendicitis. We defined a randomized trial as one in which patients were assigned prospectively to SL or SI by a random allocation. We excluded those studies that (1) focused on complicated appendicitis or those that (2) involved complicated and uncomplicated cases without differentiation of the results between the two groups. Furthermore we excluded (3) retrospective case-control studies, (4) commentaries, (5) historical technical articles, and (6) trials involving LA.

English and non-English language studies were searched and selected in the PubMed, EMBASE and Cochrane Library databases. No time limits were used. Key words used were appendicectomy, ligation, invagination, stump, complications. Articles were searched by two Authors (Gravante G, Yahia S) and classified according to those based on uncomplicated appendicitis (inflamed or suppurative appendix), complicated appendicitis (gangrenous or perforated appendix) or both. Potentially relevant studies were identified by the title and the abstract and full papers were obtained and assessed in details. The analysis of the references list allowed also the retrieval of a further pool of articles that were collected and assessed.

The methodological quality of studies retrieved was assessed independently according to the Jadad Score^[21]. Briefly, studies were scored according to the presence of three key methodological features of randomization, blinding and accountability of all patients, including withdrawals and the score ranged from 0 to 5: those that received a score of four or five were considered as highquality studies while those with a score equal to or less than three were of low quality. A specifically designed data form was used to collect all relevant data, including details of the experimental design, patients' demographics, technical aspects, outcome measures and complications. The outcome of the meta-analysis was to find eventual differences in the incidence of postoperative ileus and wound infections between the two techniques of stump invagination (SL vs SI).

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences Windows version 15.0 (SPSS, Chicago, Illinois, United States) and the Meta-analysis with Interactive eXplanations (MIX-version 1.6) program. Descriptive statistics for qualitative variables was performed with occurrences and relative frequencies,



Gravante G et al. Meta-analysis of appendiceal stump management

Table 1 Characte	eristics of s	tudies exa	amined <i>n</i> (%	%)					
Ref.	Stump closure	n	Age (yr)	Sex (male)	Jadad score ^[21]	Postoperative ileus	Wound infections	Postoperative pyrexia	Postoperative vomiting
Watter et al ^[12]	SL	44	18 (5-43)	21 (48)	1	-	8 (18.2)	-	-
	SI	59	22 (6-46)	29 (49)		-	11 (18.6)	-	-
Chaudhary et al ^[13]	SL	382	-	213 (56)	1	6 (1.6)	21 (5.5)	-	-
	SI	295	-	157 (53)		15 (5.1)	19 (6.4)	-	-
Jamal et al ^[23]	SL	40	23 ± 9	-	1	3 (7.5)	6 (15.0)	-	-
	SI	40	21 ± 6	-		11 (27.5)	9 (22.5)	-	-
Khan et al ^[24]	SL	50	24 ± 8	35 (70)	1	0	2 (4.0)	10 (20.0)	-
	SI	50	24 ± 9	32 (64)		1 (2.0)	3 (6.0)	15 (30.0)	-
Reza et al ^[25]	SL	184	27 ± 14	129 (70)	1	3 (1.6)	8 (4.2)	-	-
	SI	177	26 ± 13	124 (70)		8 (4.6)	7 (4.0)	-	-
Minhas et al ^[26]	SL	30	25 ± 2	17 (57)	0	0	2 (6.7)	-	3 (10.0)
	SI	30	25 ± 3	16 (53)		3 (10)	4 (13.3)	-	8 (26.7)
Chalya et al ^[22]	SL	43	24 ± 12	20 (47)	2	1 (2.3)	1 (2.3)	2 (4.7)	1 (2.3)
	SI	44	26 ± 15	21 (48)		5 (11.4)	2 (4.5)	3 (6.8)	2 (4.5)

SL: Simple ligation; SI: Stump invagination.



Figure 1 Flow-chart of the study selection process. RCTs: Randomized controlled trials.

those for continuous variables with the mean and standard deviation if parametric or median and range if non-parametric. Clinical outcomes and complications of patients in the SL and SI groups were evaluated with common tests used in meta-analyses: χ^2 test or Fisher's exact test for categorical variables. The weighted odds ratio (OR) for the occurrence of complications between SL and SI was also calculated. The model used for the meta-analysis was the fixed-effect and the weighting method was the Mantel Haenszel. Hetereogeneity was assessed with the funnel plots and the Bartlett's test. Results were considered significant if the probability of chance of occurrence was less than five percent (P < 0.05).

RESULTS

At the end of the selection process only seven articles met the inclusion criteria^[12,13,22-26] (Figure 1, Table 1) with 1468 patients presented, 773 in the SI and 695 in the SL group. One study only reported operating times, which were longer for the SI (45.3 ± 36.1 min) compared to the SL group (30.6 ± 33.4)^[22]. Postoperative complications consisted in wound infections (n = 103; 7%)^[12,13,22-26], il-

WJSP | www.wjgnet.com





Figure 2 Forest plot graph showing results on the analysis of postoperative among simple ligation and stump invagination. A: Ileus; B: Wound infections.

eus $(n = 56; 4^{0/0})^{[13,22-26]}$, pyrexia $(n = 39; 2^{0/0})^{[22,24]}$, vomiting $(n = 14; 1^{0/0})^{[22,26]}$, obstructions from adhesions $(n = 1; 0.1^{0/0})^{[12,13,22]}$. No cases of peritonitis^[13,22-24,26], fecal fistulas (stump leaks)^[24-26], abdominal abscesses^[12,13,22-26] or wound dehiscences^[25] were reported.

Six studies reported data on postoperative ileus^[13,22-26]. In all cases this resolved within 72 h from the operation. The incidence was 0%-7.5% in the SL group and 2.0%-27.5% in the SI group (Table 1). The analysis of pooled data showed that SL increased the risk of postoperative ileus of four times compared to SI (OR: 4.06; 95%CI: 2.14-7.70; P < 0.0001) (Figure 2A). Seven studies reported data on wound infections^[12,13,22-26]. The incidence was 2.3%-18.2% in the SL group and 4.0%-22.5% in the SI group (Table 1). The analysis of pooled data showed no significant differences in the risk of wound infections between SL and SI (OR: 1.24, 95%CI: 0.83-1.87; P = 0.30) (Figure 2B). The results of both complications were homogeneous as outlined by the funnel plots that were highly symmetrical (Q value for heterogeneity of postoperative ileus P = 0.17; Q value for heterogeneity of wound infections P = 0.98 (Figure 3).

DISCUSSION

Since the introduction of appendicectomy the treatment of the appendiceal stump has been a crucial step to determine the outcome of the operation. The proper management of the stump is important to prevent serious postoperative complications such as fecal contamination and peritonitis. After the initial introduction, the SL approach was considered not sure enough by some. Authors for an adequate closure of the stump, therefore, the invagination method was performed to avoid leaving open mucosa free in the peritoneal cavity and to favour the serosa-to-serosa contact that was believed neces-



Figure 3 Funnel plot graph showing heterogeneity analysis on postoperative among simple ligation and stump invagination. A: lleus; B: Wound infections.

sary for a proper healing. SI became fashionable at the end of the last century since it was thought to prevent adhesions (by seroserosal healing) and stump blowout (especially when the base did not seem healthy enough to support the SL approach), or at last contain it, as the leak would drain into the cecum. Theoretical advantages of SI over SL included better control of stump hemorrhages, double secure closure of the cecal wall, reduced chances of peritoneal contamination from an infected stump and reduced risk of postoperative adhesions by minimizing the extent of raw surfaces^[18]. However, a word of caution went out as the purse string technique was accused of increasing the risk of ischemia around the SI closure. Therefore, SL was indicated only in those patients where a severe inflammation and induration of the cecum could have rendered the SI approach too dangerous^[27]. At the same time the SI approach can produce peculiar complications such as intramural abscesses and erosion of the cecal wall^[28,29], or fecal fistulas from reduced blood supply to the cecal wall and local ischemia^[30]. Furthermore, in the long-term it can simulate a

cecal polyp on radiological imaging and potentially lead to unnecessary invasive tests in the screening of bowel cancers^[27,31,32].

In order to select only articles with homogeneous and comparable group of patients, we included in our meta-analysis only uncomplicated cases of appendicitis. The incidence of postoperative ileus in perforated appendicitis is between 28%-50%^[33], higher than in uncomplicated appendicitis^[34], because local inflammation and infection are major contributors. Therefore, the analysis of patients with complicated appendicitis could have biased the results achieved because the risk of ileus could have been higher in the complicated group vs the uncomplicated one. Results of the meta-analysis show that the addition of the invagination to the classic direct closure is associated with an increased risk of postoperative ileus by four times in patients with no other risk factors. Numerous hypotheses could explain the ileus pathogenesis following SI but none of them was adequately investigated experimentally. In the only study that reported the data SI took longer, a possible cause of

postoperative ileus. Additionally, the greater manipulation necessary for the invagination, or the cecum extraction through the incision to make the SI possible, could also be responsible for a serosal damage potentially combined with local ischemia. A larger incision might be necessary to perform the SI, another potential cause of postoperative ileus. Finally, the anatomical trauma on the bowel peristaltic waves deformed by the seromuscular purse-string suture or the Z-stitch, or the longer manipulation of the intestine to perform this additional step could also contribute to it.

The SI did not seem to produce specific advantages over SL regarding the other postoperative complications. Wound infection rates were similar among groups and no further comparative analysis was possible for the remaining complications due to the paucity of studies available that reported on them and the extremely low incidences (*i.e.*, peritonitis or fecal fistulas). Especially for these rare but important complications larger studies could be necessary to draw any definitive conclusions on the effects of SL or SI on its occurrence. Furthermore, appropriate studies involving only complicated cases (perforated or gangrenous appendix) should now evaluate the influence of the two techniques on postoperative complications in this higher-risk subgroup.

In the LA era results of our meta-analysis might seem less relevant, especially because cannot be applied to laparoscopic procedures in which the stump is usually fixed with endoscopic devices (i.e., Endoloops, staples). However OA remains a milestone procedure during surgical training and is still performed frequently, in some hospitals by the majority of surgeons in at least 50% of cases^[6,7]. For these reasons we focused our analysis on OAs and selected only those studies relevant for this purpose. However, one important limitation has to be acknowledged by the readers. All studies had a low Jadad score (less than 3) because of the inability to determine which methods of randomization were used in the original studies and the lack of double blinding of participants (the surgeons were always aware of the stump technique used)^[21]. More specifically, the Jadad scores were 0 (n = 1), 1 (n = 5), and 2 (n = 1). Despite the low quality of each RCT per se, studies were highly selected in order to present homogeneous and comparable groups of patients as showed by the funnel plots of the two complications. Therefore results of our meta-analysis should now form the theoretical background for future randomized studies in order to confirm the relationship found between the technique of stump closure and postoperative complications.

COMMENTS

Background

In numerous studies and meta-analyses laparoscopic appendicectomy (LA) has achieved less postoperative pain, reduced hospital stay and faster return to normal daily activities compared to open appendicectomy (OA) at the cost of longer operating times. Additionally, over OA is still necessary when LA requires conversion to an open approach.

Research frontiers

The invagination of the stump (SI) approach can produce peculiar complications such as intramural abscesses and erosion of the cecal wall, or fecal fistulas from reduced blood supply to the cecal wall and local ischemia. Furthermore, in the long-term it can simulate a cecal polyp on radiological imaging and potentially lead to unnecessary invasive tests in the screening of bowel cancers.

Innovations and breakthroughs

SI does not seem to prevent postoperative infective complications and is associated with an increased risk of ileus within the first 72 h in OAs for noncomplicated appendicitis. Appropriate studies involving only complicated cases should now evaluate the influence of the two techniques in this higher-risk subgroup and possibly find a more specific indication for the SI technique.

Applications

The meta-analysis should now form the theoretical background for future randomized studies in order to confirm the relationship found between the technique of stump closure and postoperative complications.

Peer review

The authors describe a safer technique stump ligation compared to stump imvagination. This is a well written paper with correct analysis.

REFERENCES

- Liu Z, Zhang P, Ma Y, Chen H, Zhou Y, Zhang M, Chu Z, Qin H. Laparoscopy or not: a meta-analysis of the surgical effects of laparoscopic versus open appendicectomy. *Surg Laparosc Endosc Percutan Tech* 2010; 20: 362-370 [PMID: 21150411 DOI: 10.1097/SLE.0b013e3182006f40]
- 2 Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2010; (10): CD001546 [PMID: 20927725 DOI: 10.1002/14651858.CD001546.pub3]
- 3 Markar SR, Blackburn S, Cobb R, Karthikesalingam A, Evans J, Kinross J, Faiz O. Laparoscopic versus open appendectomy for complicated and uncomplicated appendicitis in children. J Gastrointest Surg 2012; 16: 1993-2004 [PMID: 22810297 DOI: 10.1007/s11605-012-1962-y]
- 4 National Surgical Research Collaborative. Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy. *Br J Surg* 2013; 100: 1240-1252 [PMID: 23842836 DOI: 10.1002/bjs.9201]
- 5 McCartan DP, Fleming FJ, Hill AD. Patient and surgeon factors are associated with the use of laparoscopy in appendicitis. *Colorectal Dis* 2012; 14: 243-249 [PMID: 21689291 DOI: 10.1111/j.1463-1318.2011.02597.x]
- 6 Saia M, Buja A, Baldovin T, Callegaro G, Sandonà P, Mantoan D, Baldo V. Trend, variability, and outcome of open vs. laparoscopic appendectomy based on a large administrative database. *Surg Endosc* 2012; 26: 2353-2359 [PMID: 22350240 DOI: 10.1007/s00464-012-2188-5]
- 7 Vettoretto N, Gobbi S, Belli F, Corradi A, Mannino L, Ricciardelli L, Vinciguerra M, Piccolo D. Diffusion of laparoscopic appendectomies in Italy: a national audit. *Minim Invasive Ther Allied Technol* 2012; 21: 101-107 [PMID: 21417831 DOI: 10.3109/13645706.2011.557079]
- 8 Abe T, Nagaie T, Miyazaki M, Ochi M, Fukuya T, Kajiyama K. Risk factors of converting to laparotomy in laparoscopic appendectomy for acute appendicitis. *Clin Exp Gastroenterol* 2013; 6: 109-114 [PMID: 23869174 DOI: 10.2147/CEG.S41571]
- 9 Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A. Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. *Br J Surg* 2012; **99**: 1470-1478 [PMID: 23001791 DOI: 10.1002/bjs.8889]
- 10 Subramanian A, Liang MK. A 60-year literature review of stump appendicitis: the need for a critical view. *Am J Surg* 2012; 203: 503-507 [PMID: 22153086]
- 11 **Kingsley DP**. Some observations on appendicectomy with particular reference to technique. *Br J Surg* 1969; **56**: 491-496



[PMID: 4893875 DOI: 10.1002/bjs.1800560705]

- 12 Watters DA, Walker MA, Abernethy BC. The appendix stump: should it be invaginated? *Ann R Coll Surg Engl* 1984; 66: 92-93 [PMID: 6703637]
- 13 Chaudhary IA, Samiullah, Mallhi AA, Afridi Z, Bano A. Is it necessary to invaginate the stump after appendicectomy? *Pak J Med Sci* 2005; 21: 35-38
- 14 Engström L, Fenyö G. Appendicectomy: assessment of stump invagination versus simple ligation: a prospective, randomized trial. Br J Surg 1985; 72: 971-972 [PMID: 3910160 DOI: 10.1002/bjs.1800721212]
- 15 Khan S. Assessment of stump invagination versus simple ligation in open appendicectomy. *J Inst of Med* 2010; 32: 7-10 [DOI: 10.3126/joim.v32i2.3994]
- 16 Lavonius MI, Liesjärvi S, Niskanen RO, Ristkari SK, Korkala O, Mokka RE. Simple ligation vs stump inversion in appendicectomy. *Ann Chir Gynaecol* 1996; 85: 222-224 [PMID: 8950444]
- 17 Neves LJVA, Wainstein AJA, Mathias WC, Costa FPD, Costro JH, Sawassi-Rocha PR. Simple ligation or ligation and purse string invagination for the treatment of the appendiceal stump: a prospective, randomized trial. *ABCD Arq Bras Cir Dig* 2011; 24: 15-19 [DOI: 10.1590/S0102-67202011000100004]
- 18 Sinha AP. Appendicectomy: an assessment of the advisability of stump invagination. *Br J Surg* 1977; 64: 499-500 [PMID: 922311 DOI: 10.1002/bjs.1800640714]
- 19 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; **354**: 1896-1900 [PMID: 10584742 DOI: 10.1016/S0140-6736(99)04149-5]
- 20 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Metaanalysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]
- 21 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1-12 [PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4]
- 22 Chalya PL, Mchambe M. Is Invagination of Appendicular Stump in Appendicectomy Necessary? A Prospective Randomized Clinical Study. *East Cent Afr J Surg* 2012; **17**: 85-88
- 23 Jamal A, Tariq M, Khan MA, Ayyaz M. Comparison of two surgical techniques; simple ligation and ligation with invagi-

nation of appendicular stump in appendicectomy for acute appendicitis. *Pak J Med and Health Sci* 2012. Available from: URL: http://pjmhsonline.com/Comparison of two Surgical Techniques; Simple Ligation and Ligation.htm

- 24 Khan N, Bangash A, Mushtaq M, Din Sadiq MU, Muhammad I. Simple ligation versus ligation and burial of stump in appendicectomy in patients with clinical diagnosis of acute appendicitis. *JPMI* 2009; 23: 74-80
- 25 Reza AG, Bagher HM, Mansour R. Comparison of simple legation of the appendix with purse string diving appendectomy complication. *Behbood* 2011; 15: 107-111
- 26 Minhas Q, Siddique K, Mirza S, Malik AZ. Post-operative complications of stump ligation alone versus stump ligation with invagination in appendicectomy. *Int J of Surg* 2010; 22. Available from: URL: http://www.ispub.com/journal/theinternet-journal-of-surgery/volume-22-number-2/postoperative-complications-of-stump-ligation-alone-versusstump-ligation-with-invagination-in-appendicectomy.html
- 27 Maier WP, Rosemond GP. A late complication of inversion of the appendiceal stump. *Am J Surg* 1969; **118**: 467-468 [PMID: 4897742]
- 28 Cleland G. Caecocolic intussusception following appendicetomy. Br J Surg 1953; 41: 108-109 [PMID: 13082025 DOI: 10.16/0002-9610(69)90157-3]
- 29 Willis M. X. The Treatment of the appendix stump after appendectomy. *Ann Surg* 1908; 48: 74-79 [PMID: 17862201 DOI: 10.1097/0000658-190807000-00011]
- 30 Baldwin JF. The Prevention of Faecal Fistula after Appendectomy: Simple Ligation vs. Precarious Purse-String. Ann Surg 1932; 95: 704-714 [PMID: 17866768 DOI: 10.1097/000006 58-193205000-00008]
- 31 **Koff JM**, Choi JR, Hwang I. Inverted appendiceal orifice masquerading as a cecal polyp on virtual colonoscopy. *Gastrointest Endosc* 2005; **62**: 308; discussion 308 [PMID: 16047004 DOI: 10.1016/S0016-5107(05)00553-5]
- 32 Gollub MJ. Inverted appendiceal orifice masquerading as a cecal polyp on virtual colonoscopy. *Gastrointest Endosc* 2006; 63: 358 [PMID: 16427964 DOI: 10.1016/j.gie.2005.08.028]
- 33 Piskun G, Kozik D, Rajpal S, Shaftan G, Fogler R. Comparison of laparoscopic, open, and converted appendectomy for perforated appendicitis. *Surg Endosc* 2001; 15: 660-662 [PMID: 11591963 DOI: 10.1007/s004640020072]
- 34 Margenthaler JA, Longo WE, Virgo KS, Johnson FE, Oprian CA, Henderson WG, Daley J, Khuri SF. Risk factors for adverse outcomes after the surgical treatment of appendicitis in adults. *Ann Surg* 2003; 238: 59-66 [PMID: 12832966 DOI: 10.1097/01.SLA.0000074961.50020.f8]

P- Reviewers: Piccinni G, Picchio M, Sanefuji K, Tanaka K S- Editor: Qi Y L- Editor: A E- Editor: Liu XM







Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.5412/wjsp.v3.i3.54 World J Surg Proced 2013 November 28; 3(3): 54-59 ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

CASE REPORT

Epidermoid cyst of intrapancreatic accessory spleen: A case report and literature review

Chong-Lek Lee, Yang Di, Yong-Jian Jiang, Chen Jin, De-Liang Fu

Chong-Lek Lee, Yang Di, Yong-Jian Jiang, Chen Jin, De-Liang Fu, Department of Pancreatic Surgery, Pancreatic Disease Institute, HuaShan Hospital affiliated Fudan University, Shanghai 200040, China

Author contributions: Lee CL analyzed the data and wrote the paper; Jiang YJ, Di Y took part in the discussion; Jin C and Fu DL designed the research.

Correspondence to: De-Liang Fu, MD, PhD, Professor of Surgery, Chief of Department of Pancreatic Surgery, Pancreatic Disease Institute, HuaShan Hospital affiliated Fudan University, 12 WuRuMuQi Middle Road, Shanghai 200040,

China. surgeonfu@163.com

Telephone: +86-21-52888115 Fax: +86-21-62489743 Received: May 31, 2013 Revised: August 14, 2013 Accepted: September 3, 2013 Published online: November 28, 2013

Abstract

Epidermoid cyst of intrapancreatic accessory spleen is exceedingly rare; only 30 new cases have been reported in the English literature over the last 30 years. An accurate preoperative diagnosis was made in almost none of them because of the lack of reliable preoperative diagnostic methods. In this report, we present a case diagnosed with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET). A 41-year-old female who had breast cancer was routinely followed up by measuring the concentration of tumor makers. An increasing level of serum carbohydrate antigen 19-9 was detected and a cystic lesion located at the tail of pancreas was found by ultrasonography. A whole body fluorine-18 FDG positron emission tomography was performed because of a high suspicion for either a malignancy of the pancreas or a recurrence of breast cancer. No increased uptake of FDG was noted and therefore the cystic lesion was considered as pancreatic benign disease. Because pancreatic malignancy could not be entirely ruled out, distal pancreatectomy and splenectomy were performed. The final pathological diagnosis

was epidermoid cyst of intrapancreatic accessory spleen (ECIAS). The FDG-PET findings matched the histopathology. A literature review reveals that the common clinical manifestations of ECIAS include asymptomatic findings on clinical examination, an occasional increase in tumor makers on laboratory results and occurrence only in the pancreatic tail. It is often misdiagnosed due to its extreme rarity and lack of a specific radiographic sign. There is no evidence of malignancy in ECIAS. Open or laparoscopic spleen preserving distal pancreatectomy is the minimally invasive procedure that would provide the best surgical management for epidermoid cyst of intrapancreatic accessory spleen.

© 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Epidermoid cyst; Accessory spleen; Epidermoid cyst of intrapancreatic accessory spleen; Fluorodeoxyglucose positron emission tomography; Epithelial cyst

Core tip: Epidermoid cyst of intrapancreatic accessory spleen (ECIAS) is extremely rare and an accurate preoperative diagnosis is almost never made. In this article, a case diagnosed with fluorodeoxyglucose positron emission tomography scanning is presented; it is also the first case from China. A literature review of the clinical characteristics of ECIAS is also given. We suggest that open or laparoscopic spleen preserving distal pancreatectomy is the minimally invasive procedure that would provide the best surgical management for ESIAS.

Lee CL, Di Y, Jiang YJ, Jin C, Fu DL. Epidermoid cyst of intrapancreatic accessory spleen: A case report and literature review. *World J Surg Proced* 2013; 3(3): 54-59 Available from: URL: http://www.wjgnet.com/2219-2832/full/v3/i3/54.htm DOI: http:// dx.doi.org/10.5412/wjsp.v3.i3.54



INTRODUCTION

Epidermoid cyst of intrapancreatic accessory spleen (ECIAS) is extremely rare. Since 1980 when Davidson *et al*^[1] reported the first case, only $30^{[1-28]}$ new cases have been reported in the English literature. Almost none of them were accurately diagnosed preoperatively because of the lack of reliable preoperative diagnostic methods. In this article, a case diagnosed with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) scanning is presented, along with a review of the clinical characteristics of ECIAS experienced in our center and all the cases described in the English literature.

CASE REPORT

A 41-year-old Asian female who had infiltrating ductal carcinoma of the breast was treated by modified radical mastectomy on June 9, 2008 and was then routinely followed up by measuring the concentration of tumor makers. A raised level of serum carbohydrate antigen (CA) 19-9 (68.57 U/mL, reference range, less than 37 U/mL) was detected on 7th April, 2009. Four months later, the CA 19-9 level had almost doubled to 120.49 U/mL. At the same time, abdominal ultrasonography indicated a cystic lesion located at the tail of pancreas. The patient was then referred to our department for more examinations.

The patient had no symptoms of gastrointestinal or abdominal discomfort. She had no history of abdominal trauma, pancreatic insufficiency or pancreatitis. Her family history was unremarkable. Physical examination showed no abnormalities. Except for a raised level of CA 19-9, the remaining blood tests, including carcinoembryonic antigen (CEA), CA125 and serum amylase, were within normal limits. A computed tomography (CT) scan of the abdomen revealed a 4 cm round cystic lesion anterior to the spleen near the tail of the pancreas with enhancement of the cystic wall (Figure 1). Based on the raised CA 19-9 level, pancreatic tail cyst and history of breast cancer, malignancy of the pancreas or recurrence of infiltrating ductal carcinoma of the breast was highly suspected.

A whole body fluorine-18 FDG PET (Siemens Biograph 64HD, Germany) was performed. After an overnight fast, the patient had an intravenous injection of 350 MBq FDG. The patient's blood glucose level was examined just before the administration of FDG to exclude the interference factor of hyperglycemia. After 40 min of injection, emission data was obtained and the images were analyzed. The results showed that no increased uptake of FDG was detected in the whole body, including the pancreatic tail cyst, previous operative area and axillary lymph nodes (Figure 2). Based on FDG PET images, the cystic lesion was considered as pancreatic benign disease. However, 6 mo later, the CA 19-9 level had doubled again to 259.67 U/mL. She was admitted to our hospital to undergo further treatment.

Since cystic pancreatic malignancy could not be en-



Figure 1 Computed tomography scan of the abdomen revealed a 4 cm round cystic lesion (arrow) anterior to the spleen near the tail of the pancreas with enhancement of the cystic wall. A: Plain computed tomography (CT) scan; B, C: Enhanced CT scan.

tirely ruled out, the patient underwent an exploratory laparotomy, which revealed a mass of 4 cm in diameter located in the tail of pancreas. Therefore, distal pancreatectomy and splenectomy were performed. The surgical specimen contained a 4.2 cm cyst in its greatest diameter, located near the pancreatic tail (Figure 3). On histopathological examination, the cyst was filled with reddish brown fluid. Microscopically, the cyst was covered with stratified squamous epithelium and was surrounded by normal splenic tissue (Figure 4). Moreover, immunohistochemical analysis showed a strong expression of cytokeratin but Ki67, P53, Vimentin and CD56 were not expressed. The final pathological diagnosis was ECIAS.

The patient was discharged on postoperative day 11 and her serum CA 19-9 value declined to a normal level 1 mo after surgery. During the past 2 years of follow up

Lee CL et al. ECIAS: A case report and literature review

Tabl	e 1 Summary of a	all epidermoi	id cysts of intrapancreatic acce	essory spleen cases in the En	glish literature fro	m 1980	to 20	011
No	Ref.	Age/Sex	Symptoms	Preoperative diagnosis	CA 19-9 (U/mL)	Surgery	Site	Size (cm)
1	Davidson et al ^[1]	40/M	Weight loss Anorexia	Pseudocyst	NI	DPS	Tail	5.5
2	Morohoshi et al ^[2]	32/F	Left abdominal pain	Pancreatic cyst	WNL	DPS	Tail	6
3	Nakae et al ^[3]	37/F	Epigastric pain	Cystic neoplasm	NI	DPS	Tai	6.5
4	Tang et al ^[4]	38/M	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	2.3
5	Furukawa et al ^[5]	45/M	Asymptomatic	Cystic neoplasm	WNL	DP	Tail	2
6	Higaki et al ^[6]	46/F	Left back pain	Pancreatic malignancy	201	DPS	Tail	3
7	Tateyama et al ^[7]	67/F	Abdominal pain	Cystic neoplasm	WNL	DPS	Tail	3
8	Sasou et al ^[8]	49/F	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	4.3
9	Choi et al ^[9]	54/F	Epigastric discomfort	Cystic disease	NI	DPS	Tail	15
10	Tsutsumi et al ^[10]	51/M	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	2.5
11	Yokomizo et al ^[11]	38/M	Asymptomatic	Mucinous cystic neoplasm	410	DPS	Tail	2.7
12	Horibe <i>et al</i> ^[12]	48/M	Asymptomatic	Mucinous cystic neoplasm	53	DPS	Tail	2
13	Sonomura et al ^[13]	45/F	Epigastric pain	Cystic adenocarcinoma	159	DPS	Tail	3.5
14	Fink et al ^[14]	12/F	Fever	Infected abdominal cyst	NI	SPDP	Tail	10
15	Watanabe et al ^[15]	55/F	Postprandial epigastric pain	Mucinous cystic neoplasm	197	DPS	Tail	3
16	Kanazawa et al ^[16]	58/F	Asymptomatic	Mucinous cystic neoplasm	62	SPDP	Tail	2.5
17	Ru <i>et al</i> ^[17]	41/M	Asymptomatic	NI	NI	DPS	Tail	2.5
18	Itano et al ^[18]	40/M	Asymptomatic	ECIAS	WNL	DPS	Tail	4
19	Servais et al ^[19]	52/F	Asymptomatic	Pancreatic malignancy	NI	DPS	Tail	11.5
20	Gleeson et al ^[20]	32/F	Right upper quadrant pain	Cystic neoplasm	NI	DPS	Tail	1.5
21	Kadota et al ^[21]	57/F	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	6
22	Kadota et al ^[21]	70/F	Asymptomatic	Mucinous cystic neoplasm	48	DPS	Tail	1.7
23	Kadota <i>et al</i> ^[21]	37/M	Asymptomatic	Cystic neoplasm	647	SPDP	Tail	10
24	Itano et al ^[22]	67/M	Epigastric pain Weight loss	ECIAS	182	LA-	Tail	1.5
						DPS		
25	Horn <i>et al</i> ^[23]	62/M	Left abdominal pain	NI	NI	DPS	Tail	4.8
26	Iwasaki <i>et al</i> ^[24]	36/F	Asymptomatic	Mucinous cystic neoplasm	79	LA- DPS	Tail	3.4
27	Yamanishi et al ^[25]	55/F	Asymptomatic	Mucinous cystic neoplasm	90	DPS	Tail	3.3
28	Khashab et al ^[26]	49/F	Abdominal pain	PNET	NI	LA-	Tail	2.3
						SPDP		
29	Harris <i>et al</i> ^[27]	39/M	Asymptomatic	Cystic neoplasm	WNL	LA- DPS	Tail	2.5
30	Hong et al ^[28]	54/F	Abdominal discomfort	Pancreatic malignancy	WNL	SPDP	Tail	2
31	Present case	62/F	Asymptomatic	Mucinous cystic neoplasm	259	DPS	Tail	4.2

CA: Carbohydrate antigen; F: Female; M: Male; NI: Not informative; WNL: Within normal limit; DPS: Distal pancreatectomy with splenectomy; SPDP: Spleen preserving distal pancreatectomy; LA: Laparoscopic assisted.



Figure 2 Fluorine-18 fluorodeoxyglucose positron emission tomography image showed no increased uptake of fluorodeoxyglucose (arrow) detected in the cyst of pancreatic tail.

she has been doing well.

DISCUSSION

The frequency of accessory spleen is more than 10%

and nearly 20% of these are in or attached to the tail of the pancreas^[5,29]. Cystic lesions are rare in the spleen and those most frequently found are parasitic^[30]. Nonparasitic splenic cysts are histologically classified as either true or false cysts, according to the presence or absence of an epithelial lining on the inner surface^[31]. The most common nonparasitic cysts in the spleen are epidermoid cysts^[31].

Only 30 cases of ECIAS have been reported in the English literature since the first one reported by Davidson *et al*^[1] in 1980 (Table 1). ECIAS mostly occurs in middle-aged patients (average age, 47.4 years; range, 12 to 70 years). It is more common in females than males (female: male ratio, 19:12). All of the cases were found in the tail of pancreas and the size of cyst ranged from 1.5 cm to 15 cm (average, 4.35 cm). Tumor markers such as CEA and CA 19-9 (range, 48 to 647 U/mL) increase occasionally, and fall to the normal limit after excision of the lesion. It is also notable that 20 cases were from Japan, 6 from the United States, 2 from South Korea, 1 from the United Kingdom, 1 from Australia, and this is the first case from China.



Figure 3 The cut section of surgical specimen contained a 4.2 cm cyst in its greatest diameter located near the pancreatic tail. C: Cyst; AS: Accessory spleen; P: Pancreas; S: Spleen.

Rarity and nonspecific symptoms of ECIAS make it challenging for surgeons to accurately make a diagnosis prior to surgical treatment. More than half of the patients were asymptomatic and the others were admitted with complaints (9 with abdominal pain, 2 with abdominal discomfort, 2 with weight loss, 1 with left back pain, 1 with fever, and 1 with anorexia). Only 2 reported cases suspected the preoperative differential diagnosis of ECIAS^[11,18].

Several imaging techniques are available but the radiological features lack specificity to accurately identify the lesion. Abdominal ultrasonography and CT are usually the first tools which detect the lesion. However, images on abdominal ultrasound and CT scan look similar to pancreatic cystic neoplasm. This explains why most of the cases had the first preoperative clinical diagnosis of mucinous cystic neoplasm or pancreatic cystic neoplasm and were then followed by aggressive surgical management. Recently, Hu *et al*^[32] found that the diagnosis of an ECIAS should be considered when enhancing the cystic wall of the lesion in the pancreatic tail similar to the spleen during multiphasic scans in CT. The signal intensity of ECIAS is not consistent on magnetic resonance images (MRI). The cystic component occasionally shows low signal intensity on T1-weighted images and high signal intensity on T2-weighted images^[9,16,24], and sometimes it shows high signal intensity on both T1 and T2-weighted images^[18,27]. Furthermore, Motosugi *et al*^[33] suggested that in more than half of the cases of epidermoid cyst, heterotopic spleen surrounding the cyst can be detected and a noninvasive diagnosis is possible using super paramagnetic iron oxide enhanced MRI. Including the case we present, there are only 2 reported cases of ECIAS that have used fluorine-18 FDG PET scanning. Our findings showed no uptake of FDG and matched a maximum standard-uptake value (SUV) of 1.7 reported by Iwasaki, which means no evidence of malignancy^[24]. However, scanning by FDG PET could not entirely rule out malignant cystic neoplasm because false-negative results of FDG PET have also been reported^[34].

On endoscopic retrograde pancreatography (ERP)^[11,15,27],



Figure 4 Microscopically, the cyst (C) was covered with stratified squamous epithelium and was surrounded by normal splenic tissue. A fibrous capsule (FC) separates the intrapancreatic accessory spleen (AS) from pancreas (P) (HE, × 100).

endoscopic retrograde cholangiopancreatography (ERCP)^[26] and magnetic resonance cholangiopancreatography (MRCP)^[16], it has been shown that there are no communications between the cystic lesion and the pancreatic duct. Angiography shows a vascular mass^[1] which is fed by caudal pancreatic arteries^[13,16]. Endoscopic ultrasonography (EUS) suggests the existence of a cystic lesion^[11,12,15] with septa surrounded by a solid area in the tail of the pancreas^[16,20,26,27]. EUS elastography shows inhomogeneous hardness in an epidermoid cyst^[26]. Fine needle aspiration (FNA) reveals fluid with elevated CA 19-9 and CEA and points towards a possibility of pancreatic malignancy^[19,20,28].

As listed in Table 1, 25 patients received distal pancreatectomy combined with splenectomy (DPS), 5 patients received spleen preserving distal pancreatectomy (SPDP), and only 4 of these were performed with laparoscopic assistant (LA). Based on our 3 years follow up and other reported cases (from 6 to 36 mo), there is no evidence of recurrence and metastasis^[1,9,16,18,24,27,30]. ECIAS is benign and surgical treatment should be avoided when it is asymptomatic and small. However, resection should be considered for all cystic tumors of the pancreas because they are either malignant or have the potential for malignant degeneration^[35]. SPDP and LA-SPDP would be the minimally invasive treatment of choice if the possibility of malignancy could be excluded. Laparoscopic pancreatic procedures are feasible and safe in patients with benign or low grade malignancies. They also minimize blood loss and morbidity, while also reducing hospital stay and promoting early recovery^[36].

In conclusion, the common clinical manifestations of ECIAS include asymptomatic findings on clinical examination, raised levels of some tumor makers on laboratory investigations and occurrence only in the pancreatic tail. It is often misdiagnosed due to its extreme rarity and non-specific radiographic findings. There is no evidence of malignancy in ECIAS. As minimally invasive procedures, SPDP and LA-SPDP would be the best surgical management. Nevertheless, it also goes without saying that ECIAS should not be forgotten as a differential diagnosis of pancreatic cystic lesion.

REFERENCES

- Davidson ED, Campbell WG, Hersh T. Epidermoid splenic cyst occurring in an intrapancreatic accessory spleen. *Dig Dis Sci* 1980; 25: 964-967 [PMID: 7449592 DOI: 10.1007/ BF01308048]
- 2 **Morohoshi T**, Hamamoto T, Kunimura T, Yoshida E, Kanda M, Funo K, Nagayama T, Maeda M, Araki S. Epidermoid cyst derived from an accessory spleen in the pancreas. A case report with literature survey. *Acta Pathol Jpn* 1991; **41**: 916-921 [PMID: 1785350]
- 3 **Nakae Y**, Hayakawa T, Kondo T, Shibata T, Kitagawa M, Sakai Y, Sobajima H, Ishiguro H, Tanikawa M, Nimura Y. Epidermoid cyst occurring in a pancreatic accessory spleen. *J Clin Gastroenterol* 1991; **13**: 362-364 [PMID: 2066557]
- 4 **Tang X**, Tanaka Y, Tsutsumi Y. Epithelial inclusion cysts in an intrapancreatic accessory spleen. *Pathol Int* 1994; **44**: 652-654 [PMID: 7952152 DOI: 10.1111/j.1440-1827.1994. tb01726.x]
- 5 Furukawa H, Kosuge T, Kanai Y, Mukai K. Epidermoid cyst in an intrapancreatic accessory spleen: CT and pathologic findings. *AJR Am J Roentgenol* 1998; **171**: 271 [PMID: 9648813]
- 6 Higaki K, Jimi A, Watanabe J, Kusaba A, Kojiro M. Epidermoid cyst of the spleen with CA 19-9 or carcinoembryonic antigen productions: report of three cases. *Am J Surg Pathol* 1998; 22: 704-708 [PMID: 9630177 DOI: 10.1097/00000478-199 806000-00007]
- 7 Tateyama H, Tada T, Murase T, Fujitake S, Eimoto T. Lymphoepithelial cyst and epidermoid cyst of the accessory spleen in the pancreas. *Mod Pathol* 1998; 11: 1171-1177 [PMID: 9872647]
- 8 Sasou S, Nakamura S, Inomata M. Epithelial splenic cysts in an intrapancreatic accessory spleen and spleen. *Pathol Int* 1999; 49: 1078-1083 [PMID: 10632928 DOI: 10.1046/ j.1440-1827.1999.00983.x]
- 9 Choi SK, Ahn SI, Hong KC, Kim SJ, Kim TS, Woo ZH, Shin SH. A case of epidermoid cyst of the intrapancreatic accessory spleen. J Korean Med Sci 2000; 15: 589-592 [PMID: 11068999]
- 10 Tsutsumi S, Kojima T, Fukai Y, Kanoh K, Shimura T, Mochiki E, Kato R, Asao T, Kuwano H. Epidermoid cyst of an intrapancreatic accessory spleen--a case report. *Hepatogastroenterology* 2000; 47: 1462-1464 [PMID: 11100377]
- 11 Yokomizo H, Hifumi M, Yamane T, Hirata T, Terakura H, Murata K, Fujita H, Matsukane H. Epidermoid cyst of an accessory spleen at the pancreatic tail: diagnostic value of MRI. *Abdom Imaging* 2002; 27: 557-559 [PMID: 12172997 DOI: 10.1007/s00261-001-0055-2]
- 12 Horibe Y, Murakami M, Yamao K, Imaeda Y, Tashiro K, Kasahara M. Epithelial inclusion cyst (epidermoid cyst) formation with epithelioid cell granuloma in an intrapancreatic accessory spleen. *Pathol Int* 2001; **51**: 50-54 [PMID: 11148465 DOI: 10.1046/j.1440-1827.2001.01155.x]
- 13 Sonomura T, Kataoka S, Chikugo T, Hirooka T, Makimoto S, Nakamoto T, Sato M. Epidermoid cyst originating from an intrapancreatic accessory spleen. *Abdom Imaging* 2002; 27: 560-562 [PMID: 12172998 DOI: 10.1007/s00261-001-0145-1]
- 14 Fink AM, Kulkarni S, Crowley P, Crameri JA. Epidermoid cyst in a pancreatic accessory spleen mimicking an infected abdominal cyst in a child. *AJR Am J Roentgenol* 2002; 179: 206-208 [PMID: 12076937]
- 15 Watanabe H, Yamaguchi Y, Ohtsubo K, Mouri H, Motoo Y, Yamashita K, Minamoto T, Gabata T, Sawabu N. Epidermoid cyst of the intrapancreatic accessory spleen producing CA19-9. *Dig Endosc* 2004; 16: 244-248 [DOI: 10.1111/j.1443-1661.2004.00347.x]
- 16 Kanazawa H, Kamiya J, Nagino M, Uesaka K, Yuasa N, Oda K, Arai T, Nishio H, Nimura Y. Epidermoid cyst in an

intrapancreatic accessory spleen: a case report. J Hepatobiliary Pancreat Surg 2004; **11**: 61-63 [PMID: 15754048 DOI: 10.1007/s00534-003-0844-9]

- 17 Ru K, Kalra A, Ucci A. Epidermoid cyst of intrapancreatic accessory spleen. *Dig Dis Sci* 2007; **52**: 1229-1232 [PMID:17385039 DOI: 10.1007/s10620-006-9376-x]
- 18 Itano O, Shiraga N, Kouta E, Iri H, Tanaka K, Hattori H, Suzuki F, Otaka H. Epidermoid cyst originating from an intrapancreatic accessory spleen. *J Hepatobiliary Pancreat Surg* 2008; 15: 436-439 [PMID: 18670847 DOI: 10.1007/ s00534-007-1243-4]
- 19 Servais EL, Sarkaria IS, Solomon GJ, Gumpeni P, Lieberman MD. Giant epidermoid cyst within an intrapancreatic accessory spleen mimicking a cystic neoplasm of the pancreas: case report and review of the literature. *Pancreas* 2008; 36: 98-100 [PMID: 18192891 DOI: 10.1097/MPA.0b013e3181359e36]
- 20 Gleeson FC, Kendrick ML, Chari ST, Zhang L, Levy MJ. Epidermoid accessory splenic cyst masquerading as a pancreatic mucinous cystic neoplasm. *Endoscopy* 2008; 40 Suppl 2: E141-E142 [PMID: 18633876 DOI: 10.1055/s-2007-995735]
- 21 Kadota K, Kushida Y, Miyai Y, Katsuki N, Hayashi T, Bando K, Shibuya S, Haba R. Epidermoid cyst in an intrapancreatic accessory spleen: three case reports and review of the literatures. *Pathol Oncol Res* 2010; 16: 435-442 [PMID: 19949910 DOI: 10.1007/s12253-009-9229-y]
- 22 Itano O, Chiba N, Wada T, Yuasa Y, Sato T, Ishikawa H, Koyama Y, Matsui H, Kitagawa Y. Laparoscopic resection of an epidermoid cyst originating from an intrapancreatic accessory spleen: report of a case. *Surg Today* 2010; 40: 72-75 [PMID: 20037845 DOI: 10.1007/s00595-009-4006-9]
- 23 **Horn AJ**, Lele SM. Epidermoid cyst occurring within an intrapancreatic accessory spleen. A case report and review of the literature. *JOP* 2011; **12**: 279-282 [PMID: 21546709]
- 24 Iwasaki Y, Tagaya N, Nakagawa A, Kita J, Imura J, Fujimori T, Kubota K. Laparoscopic resection of epidermoid cyst arising from an intrapancreatic accessory spleen: a case report with a review of the literature. *Surg Laparosc Endosc Percutan Tech* 2011; 21: e275-e279 [PMID: 22002295 DOI: 10.1097/SLE.0b013e31822dd14a]
- 25 Yamanishi H, Kumagi T, Yokota T, Koizumi M, Azemoto N, Watanabe J, Mizuno Y, Sugita A, Abe M, Ikeda Y, Matsuura B, Hiasa Y, Onji M. Epithelial cyst arising in an intrapancreatic accessory spleen: a diagnostic dilemma. *Intern Med* 2011; 50: 1947-1952 [PMID: 21921374]
- 26 Khashab MA, Canto MI, Singh VK, Hruban RH, Makary MA, Giday S. Endosonographic and elastographic features of a rare epidermoid cyst of an intrapancreatic accessory spleen. *Endoscopy* 2011; 43 Suppl 2 UCTN: E193-E194 [PMID: 21590599 DOI: 10.1055/s-0030-1256272]
- 27 Harris AC, Chaudry MA, Menzies D, Conn PC. Laparoscopic resection of an epidermoid cyst within an intrapancreatic accessory spleen: a case report and review article. *Surg Laparosc Endosc Percutan Tech* 2012; 22: e246-e249 [PMID: 22874714 DOI: 10.1097/SLE.0b013e31825b3761]
- 28 Hong R, Choi N, Sun K, Lim S, Han Y. Epidermoid cyst arising from an intrapancreatic accessory spleen: A case report and review of the literature. *Oncol Lett* 2013; 5: 469-472 [PMID: 23420784]
- 29 Halpert B, Alden ZA. Accessory spleens in or at the tail of the pancreas. A survey of 2700 additional necropsies. *Arch Pathol* 1964; 77: 652-654 [PMID: 14130052]
- 30 **Bürrig KF**. Epithelial (true) splenic cysts. Pathogenesis of the mesothelial and so-called epidermoid cyst of the spleen. *Am J Surg Pathol* 1988; **12**: 275-281 [PMID: 3354753]
- 31 McClure RD, Altemeier WA. CYSTS OF THE SPLEEN. *Ann* Surg 1942; **116**: 98-102 [PMID: 17858077]
- 32 Hu S, Zhu L, Song Q, Chen K. Epidermoid cyst in intrapancreatic accessory spleen: computed tomography findings and clinical manifestation. *Abdom Imaging* 2012; 37: 828-833 [PMID: 22327420]



- 33 Motosugi U, Yamaguchi H, Ichikawa T, Sano K, Araki T, Takayama Y, Shimizu K, Hatori T, Shiratori K, Koyama I, Shimizu M. Epidermoid cyst in intrapancreatic accessory spleen: radiological findings including superparamagnetic iron oxide-enhanced magnetic resonance imaging. J Comput Assist Tomogr 2010; 34: 217-222 [PMID: 20351508 DOI: 10.1097/RCT.0b013e3181c1b2bd]
- 34 **Inokuma T**, Tamaki N, Torizuka T, Magata Y, Fujii M, Yonekura Y, Kajiyama T, Ohshio G, Imamura M, Konishi J. Evaluation of pancreatic tumors with positron emission

Lee CL et al. ECIAS: A case report and literature review

tomography and F-18 fluorodeoxyglucose: comparison with CT and US. *Radiology* 1995; **195**: 345-352 [PMID: 7724751]

- 35 Warshaw AL, Compton CC, Lewandrowski K, Cardenosa G, Mueller PR. Cystic tumors of the pancreas. New clinical, radiologic, and pathologic observations in 67 patients. *Ann Surg* 1990; 212: 432-433; discussion 444-445 [PMID: 2171441]
- 36 Iacobone M, Citton M, Nitti D. Laparoscopic distal pancreatectomy: up-to-date and literature review. World J Gastroenterol 2012; 18: 5329-5337 [PMID: 23082049 DOI: 10.3748/wjg. v18.i38.5329]

P- Reviewer: Treglia G S- Editor: Song XX L- Editor: Roemmele A E- Editor: Liu XM





World Journal of WUSP Surgical Procedures

Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com www.wjgnet.com World J Surg Proced 2013 November 28; 3(3): I-V ISSN 2219-2832 (online) © 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Surgical Procedures (World J Surg Proced, WJSP, online ISSN 2219-2832, DOI: 10.5412) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WISP covers topics concerning ambulatory surgical procedures, cardiovascular surgical procedures, digestive system surgical procedures, endocrine surgical procedures, obstetric surgical procedures, neurosurgical procedures, ophthalmologic surgical procedures, oral surgical procedures, orthopedic procedures, otorhinolaryngologic surgical procedures, reconstructive surgical procedures, thoracic surgical procedures, urogenital surgical procedures, computer-assisted surgical procedures, elective surgical procedures, and minimally invasive, surgical procedures, specifically including ablation techniques, anastomosis, assisted circulation, bariatric surgery, biopsy, body modification, non-therapeutic, curettage, debridement, decompression, deep brain stimulation, device removal, dissection, drainage, electrosurgery, extracorporeal circulation, hemostasis, intraoperative care, laparotomy, ligation, lymph node excision, mastectomy, microsurgery, monitoring, intraoperative, ostomy, paracentesis, pelvic exenteration, perioperative care, postoperative care, preoperative care, prosthesis implantation, reoperation, second-look surgery, splenectomy, suture techniques, symphysiotomy, tissue and organ harvesting, transplantation, diagnostic imaging, and endoscopy. The current columns of WJSP include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography.

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

WJSP is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 OA clinical medical journals, including 41 in English, has a total of 15 471 editorial borad members or peer reivewers, and is a world first-class publisher.

Columns

The columns in the issues of WJSP will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to

write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cuttingedge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers; (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, etc.; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in surgical procedures; (12) Brief Articles: To briefly report the novel and innovative findings in surgical procedures; (13) Meta-Analysis: Covers the systematic review, mixedtreatment comparison, meta-regression, and overview of reviews, in order to summarize a given quantitative effect, e.g., the clinical effectiveness and safety of clinical treatments by combining data from two or more randomized controlled trials, thereby providing more precise and externally valid estimates than those which would stem from each individual dataset if analyzed separately from the others; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in WJSP, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of surgical procedures; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.



Instructions to authors

Name of journal World Journal of Surgical Procedures

ISSN 2219-2832 (online)

Launch date December 29, 2011

Frequency Four-monthly

Editor-in-Chief

Massimo Chello, MD, Professor, Department of Cardiovascular Sciences, University Campus Bio Medico of Rome, Via Alvaro Del Portillo 200, 00128 Rome, Italy

Feng Wu, MD, PhD, Professor, Nuffield Department of Surgical Sciences, University of Oxford, Level 6, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, United Kingdom

Editorial office

Jin-Lei Wang, Director Xiu-Xia Song, Vice Director *World Journal of Surgical Procedures* Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China Telephone: +86-10-85381891 Fax: +86-10-85381893 E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

Publisher

Baishideng Publishing Group Co., Limited Flat C, 23/F, Lucky Plaza, 315-321 Lockhart Road, Wan Chai, Hong Kong, China Telephone: +852-31779906 Fax: +852-65557188 E-mail: bpgoffice@wignet.com http://www.wignet.com

Production center

Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China Telephone: +86-10-85381892 Fax: +86-10-85381893

Representative office

USA Office 8226 Regency Drive, Pleasanton, CA 94588-3144, United States

Instructions to authors

Full instructions are available online at http://www.wignet.com/2219-2832/g_info_20100722180909.htm.

Indexed and Abstracted in

Digital Object Identifier.

SPECIAL STATEMENT

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

Biostatistical editing

Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-

squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJSP* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje. org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

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, Discus-



sion, 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 Baishideng Publishing Group Co., Limited, 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 copyedit 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 ICMJE 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/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2219-2832/g_info_20100722180909.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to bpgoffice@wjgnet.com, or by telephone: +86-10-85381892. 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 ICMJE, 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: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/..."), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; 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), and CONCLUSION (no more than 26 words).

Key words

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

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRO-DUCTION, 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.

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. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of

WJSP | www.wjgnet.com

Instructions to authors

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 E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, ec., 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 ^c*P* < 0.05 and ^f*P* < 0.01. Other notes in tables or under illustrations should be expressed as ¹F, ³F; 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 •, \circ , •, •, \Box , \triangle , *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)
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/wig.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

- 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
- 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:10.10 97/00003086-200208000-00026]

No volume or issue

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

Books

Personal author(s)

- 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/index.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 \pm SD or mean \pm 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) = $8.6 \ 24.5 \ \mu g/L$; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formal-dehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23243641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2219-2832/g_info_20100725073806.htm.

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*.

Examples for paper writing

All types of articles' writing style and requirement will be found in the

link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system *via* the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

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; and (4) Grade D: rejected. Revised articles should reach Grade A.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2219-2832/g_info_20100725073726.htm.

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/2219-2832/g_info_20100725073445.htm.

Proof of financial support

For papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

STATEMENT ABOUT ANONYMOUS PUBLICA-TION OF THE PEER REVIEWERS' COMMENTS

In order to increase the quality of peer review, push authors to carefully revise their manuscripts based on the peer reviewers' comments, and promote academic interactions among peer reviewers, authors and readers, we decide to anonymously publish the reviewers' comments and author's responses at the same time the manuscript is published online.

PUBLICATION FEE

WJSP is an international, peer-reviewed, OA online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium and format, provided the original work is properly cited. The use is non-commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. All invited articles are published free of charge.





Published by Baishideng Publishing Group Co., Limited

Flat C, 23/F., Lucky Plaza, 315-321 Lockhart Road, Wan Chai, Hong Kong, China Fax: +852-65557188 Telephone: +852-31779906 E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

