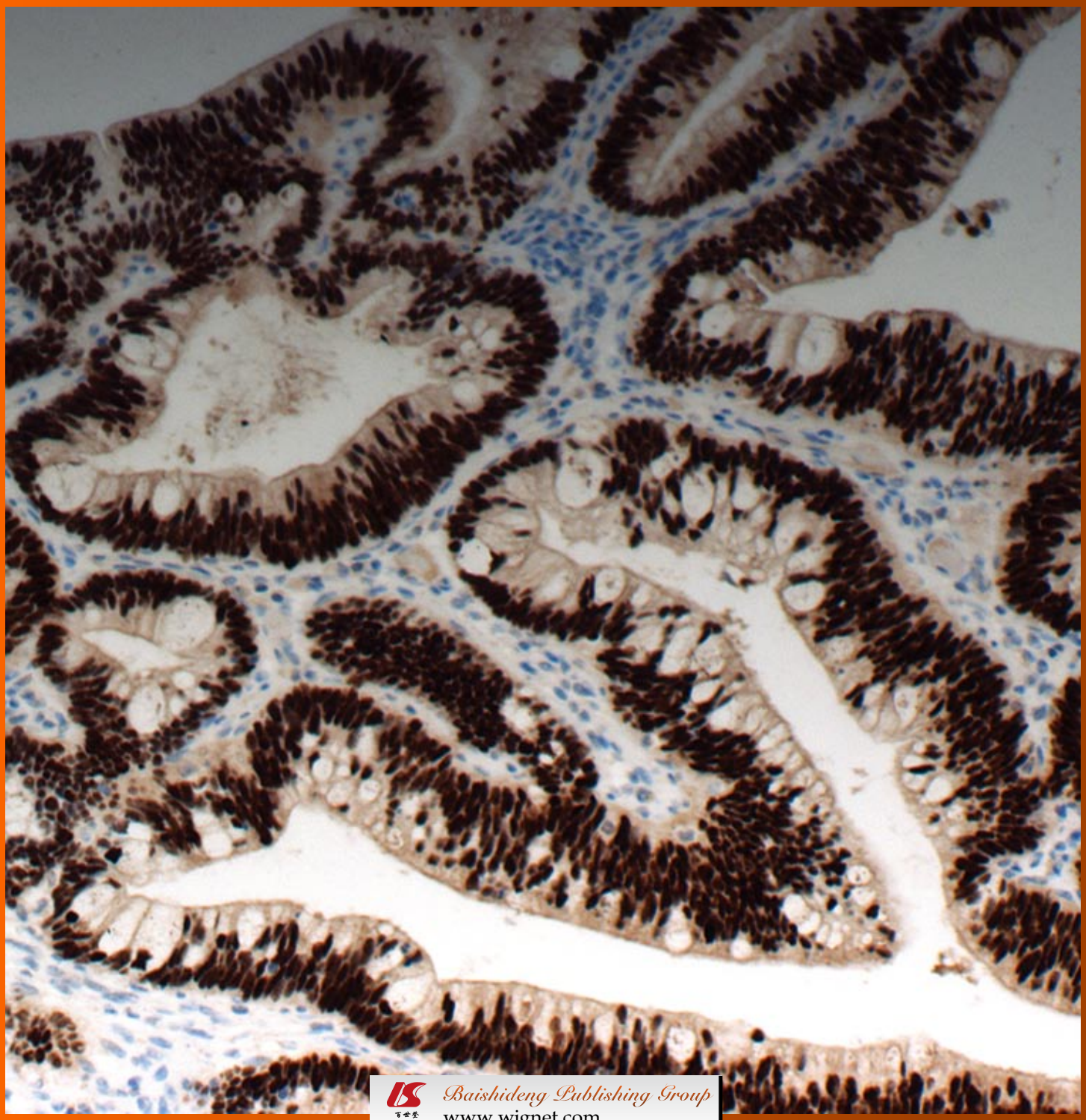
ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2011 November 27; 3(11): 159-182



Baishideng Publishing Group
www.wjgnet.com

WJGS World Journal of Gastrointestinal Surgery

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

Editorial Board

2009-2013

The *World Journal of Gastrointestinal Surgery* Editorial Board consists of 336 members, representing a team of worldwide experts in gastrointestinal surgery research. They are from 35 countries, including Australia (6), Austria (2), Belgium (6), Brazil (9), Bulgaria (2), Canada (8), China (30), Denmark (1), Finland (1), France (10), Germany (22), Greece (6), India (10), Ireland (3), Israel (3), Italy (48), Jamaica (1), Japan (47), Malaysia (1), Netherlands (9), Pakistan (1), Poland (1), Portugal (1), Russia (1), Singapore (6), Serbia (1), South Korea (9), Spain (5), Sweden (2), Switzerland (4), Thailand (2), Tunisia (1), Turkey (8), United Kingdom (7), and United State (62).

France

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

Germany

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

Greece

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

India

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

Ireland

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

Israel

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

Italy

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

Jamaica

Joseph M Plummer, *Kingston*

Japan

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

Malaysia

Way Seah Lee, *Kuala Lumpur*

Netherlands

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

Pakistan

Kamran Khalid, *Lahore*

WJGS

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 3 Number 11 November 27, 2011

World Journal of Gastrointestinal Surgery
Volume 3 Number 11 November 27, 2011

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

LAUNCH DATE
November 30, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Gastrointestinal Surgery*.
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1891
Fax: +86-10-8538-1893
E-mail: wjgs@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
November 27, 2011

ISSN
ISSN 1948-9366 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Gastrointestinal Surgery
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1891
Fax: +86-10-8538-1893
E-mail: wjgs@wjgnet.com
http://www.wjgnet.com

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-9366/g_info_20100305152206.htm.

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

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v3.i11.159

World J Gastrointest Surg 2011 November 27; 3(11): 159-166
ISSN 1948-9366 (online)

EDITORIAL

CDX2 as a marker for intestinal differentiation: Its utility and limitations

Reda S Saad, Zeina Ghorab, Mahmoud A Khalifa, Mei Xu

Reda S Saad, Zeina Ghorab, Mahmoud A Khalifa, Department of Pathobiology, Sunnybrook Health Sciences Center, University of Toronto, Ontario, ON M4N 3M5, Canada
Mei Xu, Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, ON M4N 3M5, Canada
Author contributions: All authors contributed to this review.
Correspondence to: Reda S Saad, MD, PhD, FRCPC, Associate Professor, Department of Pathobiology, Rm E403, Sunnybrook Health Sciences Center, 2075 Bayview Avenue, Toronto, Ontario, ON M4N 3M5, Canada. reda.saad@sunnybrook.ca
Telephone: +1-416-4804011 Fax: +1-416-4804271
Received: September 21, 2011 Revised: November 3, 2011
Accepted: November 10, 2011
Published online: November 27, 2011

Key words: CDX2; Colorectal carcinoma; Aberrant expression

Peer reviewer: Yong-Song Guan, MD, PhD, Professor, Department of Oncology and Radiology, State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China

Saad RS, Ghorab Z, Khalifa MA, Xu M. CDX2 as a marker for intestinal differentiation: Its utility and limitations. *World J Gastrointest Surg* 2011; 3(11): 159-166 Available from: URL: http://www.wjgnet.com/1948-9366/full/v3/i11/159.htm DOI: http://dx.doi.org/10.4240/wjgs.v3.i11.159

Abstract

CDX2 is a nuclear homeobox transcription factor that belongs to the caudal-related family of CDX homeobox genes. The gene encoding CDX2 is a nonclustered hexapeptide located on chromosome 13q12-13. Homeobox genes play an essential role in the control of normal embryonic development. CDX2 is crucial for axial patterning of the alimentary tract during embryonic development and is involved in the processes of intestinal cell proliferation, differentiation, adhesion, and apoptosis. It is considered specific for enterocytes and has been used for the diagnosis of primary and metastatic colorectal adenocarcinoma. CDX2 expression has been reported to be organ specific and is normally expressed throughout embryonic and postnatal life within the nuclei of epithelial cells of the alimentary tract from the proximal duodenum to the distal rectum. In this review, the authors elaborate on the diagnostic utility of CDX2 in gastrointestinal tumors and other neoplasms with intestinal differentiation. Limitations with its use as the sole predictor of a gastrointestinal origin of metastatic carcinomas are also discussed.

INTRODUCTION

CDX2 is a nuclear homeobox transcription factor that belongs to the caudal-related family of CDX homeobox genes[1-3]. The gene encoding CDX2 is a nonclustered hexapeptide located on chromosome 13q12-13[1,2]. Homeobox genes play an essential role in the control of normal embryonic development[1,2]. CDX2 is crucial for axial patterning of the alimentary tract during embryonic development[4,5] and is involved in the processes of intestinal cell proliferation, differentiation, adhesion, and apoptosis[4-6]. CDX2 functions within the cell to induce differentiation and inhibit proliferation at the level of gene transcription[4]. It stimulates intestinal epithelium differentiation through activating the transcription of proteins specific to the intestine, such as MUC2, sucrase, isomaltase, and carbonic anhydrase I[4,5]. CDX2 inhibits epithelial proliferation through upregulating WAF1/p21, a cdk inhibitor that arrests the cell cycle upon DNA damage[6]. CDX2 expression has been reported to be organ specific and is normally expressed throughout embryonic and postnatal life within the nuclei of epithelial cells of the alimentary tract from the proximal duodenum to the distal rectum[4-7].

The majority of homeobox genes are considered as proto-oncogenes, with few exceptions[8]. Expression of CDX2 decreases in human colorectal cancers in proportion to the tumor grade and it is lost in minimally differentiated colon carcinomas[9]. In addition, CDX2 is downregulated by oncogenic pathways in colon cancer cells. These observations have suggested that CDX2 has a tumor suppressor function. In addition, Bonhomme *et al*[8] have provided experimental evidence that *CDX2* is a colon tumor suppressor gene. Unlike other colon tumor suppressor genes such as *APC* and *p53*[10], which act also outside the gut, CDX2 is the first intestine-specific tumor suppressor[8].

Since CDX2 is a transcription factor, it shows a nuclear immunostaining pattern. In practice, nuclear expression of transcription factors has several distinct advantages over cytoplasmic "differentiation" markers. Firstly, transcription factors generally yield an "all or none" signal, with the vast majority of positive cases containing positive signal in > 90% of the target cell population. Secondly, the nuclear localization of the signal is much less likely to be confused with biotin or other sources of false-positive cytoplasmic signals. Third, there is no association between the levels of expression of nuclear transcription factors and the state of differentiation of the tumor.

CDX2 EXPRESSION IN GASTROINTESTINAL TUMORS

CDX2 expression in colorectal carcinoma

CDX2 is expressed in normal small and large intestinal epithelial cells, including absorptive, endocrine and Paneth cells[4]. Recent immunohistochemical studies have reported that CDX2 is a specific and sensitive marker for adenocarcinoma of the gastrointestinal tract, particularly colorectal adenocarcinoma[7,11-14]. Moskaluk *et al*[12], examined CDX2 expression in tissue microarrays containing 745 cancers from many anatomic sites and observed strong positive staining in 90% of colonic adenocarcinomas, 20%-30% of carcinomas of the stomach, esophagus and ovary (limited to endometrioid and mucinous types) and in less than 1% of all other carcinoma types. Another study conducted by De Lott *et al*[13], investigated CDX2 expression in tissue microarrays from 71 colorectal adenocarcinomas, 47 lung adenocarcinomas, 31 hepatocellular carcinomas, 55 squamous cell carcinomas of the lung, 69 neuroendocrine carcinomas of the lung, 43 neuroendocrine carcinomas of the pancreas, 57 pancreatic adenocarcinomas, and 256 endometrial adenocarcinomas. Positive results were found in about 72% of colorectal cancers and in only 6% of endometrial carcinomas[13]. Tumors from other sites were either negative or rarely positive. Similarly, Werling *et al*[14] found CDX2 expression in the majority of colorectal carcinomas, with only few exceptions. A heterogeneous focal staining pattern was found in pancreatic, gastric and gastroesophageal adenocarcinomas and cholangiocarcinomas. CDX2 was rarely expressed in carcinomas of the breast, genitourinary tracts, gynecologic tracts, lung, head and neck[14]. Bakaris *et al*[15] observed that CDX2 expression was seen in all cases of colonic adenoma, and the majority of colorectal adenocarcinomas. These previous studies have illustrated the value of CDX2 expression in determining tumor origin in the diagnostic settings[12].

Previous studies have reported a wide variation in the proportion of colorectal adenocarcinomas that express CDX2. Some studies have reported its expression in 98% to 100% of cases, while others have observed loss of CDX2 expression in 14% to 37% of cases[7, 12,16]. Loss of CDX2 expression in colorectal cancer has been found to correlate with high tumor grade, microsatellite instability or advanced tumor stage[7,15,17]. Considering the role of CDX2 in promoting cellular differentiation and inhibiting proliferation[2,3], loss of CDX2 expression could conceivably contribute to aggressive tumor behavior and increase the likelihood of metastatic disease[17]. Choi *et al*[18] analyzed the expression of CDX2 in 123 cases of sporadic colorectal cancers and found loss of its expression in 29/123 (23.6%) specimens. Again, this loss of expression was found to correlate with higher tumor stage and positive lymph node metastasis[18]. Loss of CDX2 is also more frequently encountered in mismatch repair-deficient colorectal cancer[9]. Utilizing a database of 621 colorectal cancers, Baba *et al*[9] found that CDX2 loss was correleted directly with female gender, high tumor grade, stage IV disease, and inversely with LINE-1 hypomethylation, p53 expression, and β-catenin activation. CDX2 loss was associated with high overall mortality among patients with a family history of colorectal cancer[9]. This implies the importance of CDX2 in the suppression of tumorgenesis in a subset of colorectal cancers and its potential for use as a prognostic marker in identifying high risk patients.

Rectal adenocarcinomas are commonly lumped together with colonic tumors, making their proper immunoprofiling difficult[19]. We recently investigated the expression of CDX2, along with CK7 and CK20, in rectal adenocarcinoma. In our experience, CDX2 was expressed in the majority of cases of rectal adenocarcinoma, and staining was predominantly nuclear with occasional faint cytoplasmic staining[19]. In our study, CDX2 expression did not appear to correlate with tumor grade (tumor differentiation).

CDX2 expression in esophageal neoplasms

CDX2 is not expressed in normal esophageal and gastric epithelial cells but is expressed in intestinal metaplasia of the esophagus[20-22]. In some patients, Barrett's esophagus is complicated by the development of esophageal adenocarcinoma[20,21]. Lord *et al*[22] investigated the expression of CDX2 and PITX1 in Barrett's esophagus and associated adenocarcinoma. Negative CDX2 staining was observed in normal squamous esophageal lining, while strong (3+) nuclear staining was seen in all cases of Barrett's intestinal metaplasia, dysplasia, and associated adenocarcinoma[22]. The level of CDX2 mRNA expression was found to co-

incide with immunohistochemical CDX2 expression as both were upregulated in Barrett's intestinal metaplasia tissues and remained elevated in dysplastic and adenocarcinoma cells[22]. In contrast, a recent study has reported CDX2 expression which was significantly weaker or absent in esophageal dysplasia and adenocarcinoma in comparison to metaplastic cells[23].

CDX2 expression in gastric adenocarcinoma

Gastric carcinoma is frequently found in association with intestinal metaplasia[24]. Studies have reported CDX2 expression in both intestinal metaplasia of the stomach and intestinal-type gastric carcinoma[25-31]. Furthermore, incomplete intestinal metaplasia, which expresses both gastric and intestinal mucins, shows lower CDX2 expression compared with complete intestinal metaplasia[32]. Although incomplete intestinal metaplasia morphologically resembles colon, its CDX2 expression was apparently lower than that seen in the normal colon. Similar to esophageal dysplasia, previous studies showed decreasing CDX2 expression from metaplasia to dysplasia to adenocarcinoma[32]. Intestinal metaplasia or dysplasia with low expression of CDX2 may potentially serve as predictive markers for gastric cancer[32].

Song *et al*[33] reported a significantly better outcome for CDX2-positive gastric tumors over CDX2-negative tumors. Other studies have similarly demonstrated that positive CDX2 expression in gastric cancer significantly correlated with better differentiation and prognosis[34,35]. CDX2 expression has been evaluated in 69 cases of gastric epithelial dysplasia, 88 early gastric cancers and 56 advanced gastric cancers. Increased CDX2 expression was more frequently associated with adenomatous-type gastric epithelial dysplasia (87%), compared with the foveolar (47%) or hybrid (44%) types. CDX2 expression levels also gradually decreased from gastric dysplasia, to early and advanced gastric cancers. Moreover, a negative correlation was observed between CDX2 expression and the depth of tumor invasion[26]. A recent study showed that absence of nuclear CDX2 expression may serve as a powerful predictor of lymph node metastasis in gastric cancer[36]. Overexpression of CDX2 has recently been shown to inhibit cell growth and proliferation *in vitro* and can effectively inhibit gastric cancer progression, making this a potential therapeutic target[37].

CDX2 expression in small intestinal adenocarcinoma

Despite the large surface area, malignancies of the small intestine are quite rare and account for only 2% of primary gastrointestinal tumors[38]. Small intestinal adenocarcinoma shows similarities in morphology and risk factors with its colorectal counterpart[38]. However, it has been found to be immunophenotypically distinct from colorectal adenocarcinoma. Zhang *et al*[38] examined the expression of CDX2 in small intestinal adenocarcinoma and found that CDX2 was expressed in 60% of cases of small intestinal adenocarcinoma in comparison to 98% of colorectal adenocarcinoma.

CDX2 expression in gallbladder adenocarcinoma

Gallbladder adenocarcinoma is a highly malignant neoplasm with variable incidence depending on gender and geographic distribution[39]. Sakamoto *et al*[40] investigated the expression of CDX2 in human gallbladders with cholelithiasis and reported CDX2 expression in 92% of gallbladder intestinal metaplasias. CDX2 expression has been found in dysplasia, carcinoma and intestinal metaplasia of the gallbladder and carcinogenesis may proceed through intestinal metaplasia as seen in esophageal metaplasia[39,40].

Wu *et al*[39] examined the expression of CDX2 in 68 primary gallbladder carcinomas and compared its expression with various clinicopathologic factors. Positive staining was observed in 25/68 (36.8%) cases with no significant correlation with clinicopathologic prognostic parameters. Well-differentiated carcinomas had high CDX2 expression (54.8%) compared to moderately differentiated (7.1%) and poorly differentiated carcinomas (0%)[39]. In contrast, Chang *et al*[41] reported CDX2 positivity in 29% of their cases and that expression was an independent prognostic factor in patients with biliary tract carcinoma.

CDX2 expression in extrahepatic bile duct and pancreatic adenocarcinoma

Hong *et al*[42] found CDX2 expression in 37% of their extrahepatic bile duct carcinoma cases. They observed more frequent CDX2 expression in tumors with papillary growth (60%) than in those with a nodular (25%) or infiltrative (34.9%) pattern. CDX2 expression was also more frequent in cases without vascular invasion (41.3%) than in those with vascular invasion (23%). In univariant analysis, CDX2/MUC2 positive patients had a significantly higher survival rate than negative patients[42].

CDX2 expression is focal and patchy in normal pancreatic epithelium[20] and CDX2 is infrequently expressed in pancreatic adenocarcinoma. In our experience, CDX2 is focally expressed in less than 10% of pancreatic duct adenocarcinomas[19]. Another report found CDX2 expression in only 3 of the 57 (5%) pancreatic adenocarcinoma cases studied[13]. In general, the staining pattern is usually focal and less intense than that found in colorectal adenocarcinoma.

CDX2 expression in gastrointestinal neuroendocrine tumors

We have also examined the use of CDX2 and TTF1 in differentiating metastatic neuroendocrine neoplasms of unknown origin[43]. Expression of CDX2 was found in 28/60 (47%) gastrointestinal neuroendocrine tumors with high prevalence in ileal, appendiceal and colonic origin[43] (Figure 1). Similarly, previous studies documented exclusive positive staining for CDX2 in ileal and appendiceal neuroendocrine tumors, while all rectal, gastric and duodenal neuroendocrine tumors were negative[44,45]. No CDX2 expression was observed in neuroendocrine tumors of other origins, including skin, ovary or thymus[43].

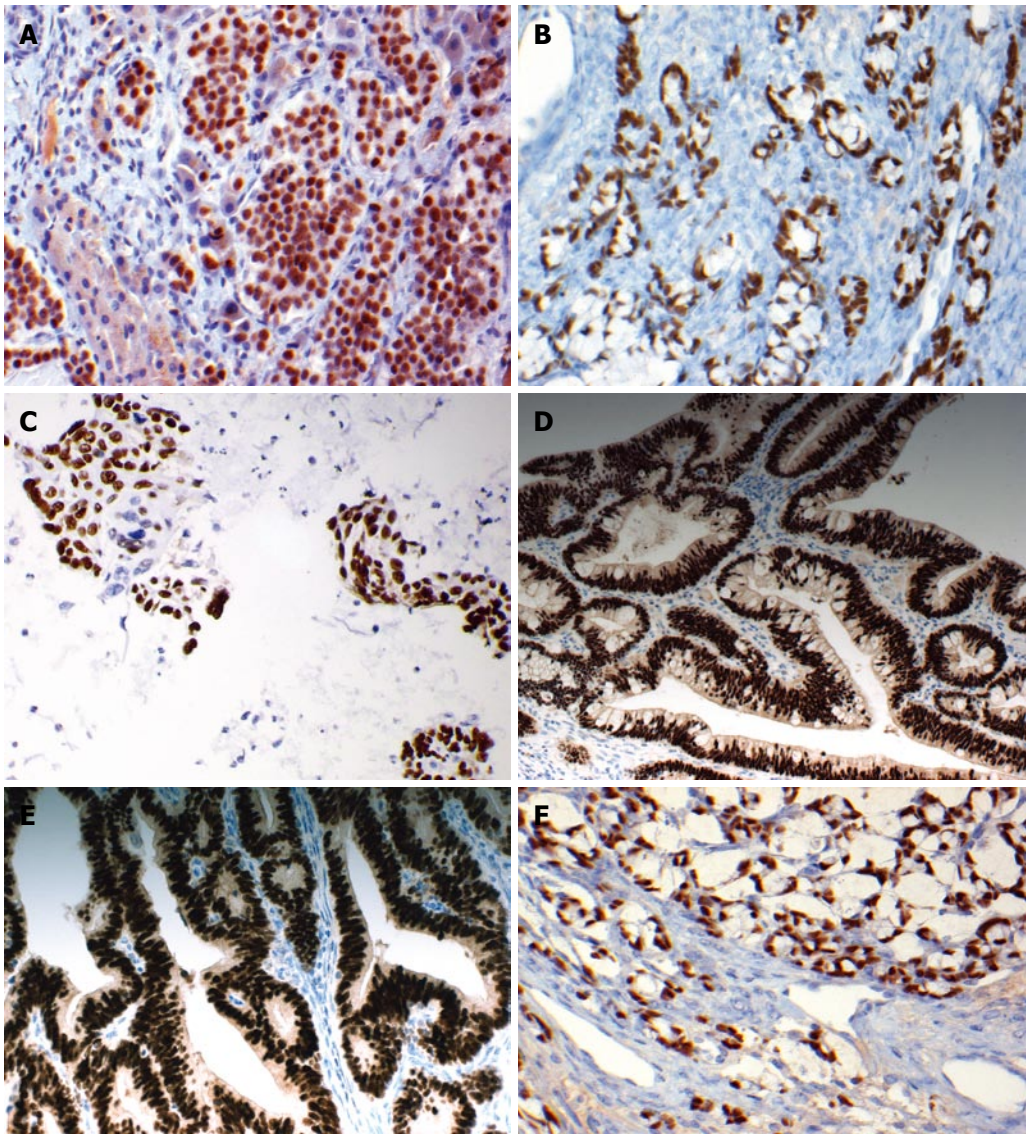


Figure 1 CDX2 expression. A: CDX2 expression in metastatic ileal carcinoid to the liver. Please note the presence of moderate nuclear staining; B: CDX2 expression is also seen in appendiceal goblet carcinoid (Immunohistochemistry × 400); C: CDX2 expression in cytology specimens of metastatic colonic carcinoma to the lung, supporting their colorectal origin. (Immunohistochemistry × 250); D: CDX2 expression is seen in the majority of endocervical adenocarcinomas of intestinal type (Immunohistochemistry × 400); E: CDX2 expression in endometrioid carcinoma (Immunohistochemistry × 400); F: CDX2 expression in sinonasal adenocarcinoma of intestinal type (Immunohistochemistry × 400).

Pancreatic endocrine tumors show focal and heterogeneous staining for CDX2[43].

Rabban *et al*[46] have evaluated CDX2 expression in metastatic and primary ovarian carcinoids. They reported diffuse nuclear CDX-2 expression in majority of primary ovarian and metastatic intestinal carcinoids involving the ovary, particularly insular and mucinous types. They concluded that CDX2 is not specific and cannot be used to determine the site of ovarian carcinoids. All primary ovarian carcinoids were negative for TTF-1, CK7 and CK20[46].

USE OF CDX2 TO CONFIRM METASTATIC ADENOCARCINOMA OF A GASTROINTESTINAL ORIGIN

CDX2 immunohistochemical staining for diagnosis of metastatic adenocarcinoma has recently come into practice[47-49]. Due to its limited expression in the spectrum of human tissues and neoplasia, CDX2 has been investigated for its usefulness in diagnosing a metastatic adenocarcinoma as being of a gastrointestinal origin[47-49].

The diagnostic utility of CDX2 as a marker to identify the gastrointestinal origin of a metastatic tumor was addressed a study where we used CDX2 to distinguish bronchioloalveolar adenocarcinoma of the lung from metastatic mucinous colorectal adenocarcinoma[42]. Using surgical material, Saad *et al*[47] and Barbareschi *et al*[49] both found CDX2 expression in metastatic colorectal adenocarcinoma to the lung compared but absent in primary lung adenocarcinoma. Similarly, CDX2 was useful in cytology specimens as a marker of metastatic gastrointestinal adenocarcinoma when compared to other metastatic tumors (Figure 1C). CDX2 expression was

found in 19/22 (86%) confirmed metastatic gastrointestinal specimens[50]. All other metastatic adenocarcinomas, from lung, breast, ovaries, pancreas, and prostate sites, were negative for CDX2[50]. Similarly, Lora and Kanitakis investigated CDX2 expression in 68 cutaneous metastatic tumors of various origin and found that CDX2 was a specific immunohistochemical marker for cutaneous metastases from intestinal and urothelial carcinomas[48].

Expression of CDX2 tumors outside the colorectum has been reported[12,14]. Tot[51] reported that the CK20+/CK7- pattern is more specific than CDX2 expression in predicting the colorectal origin of metastatic adenocarcinoma. It is usually recommended to use CDX2 as a part of immunostaining panel including CK7, CK20, mCEA and villin to prove the intestinal origin of a metastatic tumor[50].

DIAGNOSTIC DILEMMAS WITH ABERRANT CDX2 EXPRESSION

Despite the relatively restricted CDX2 expression profile, expression of CDX2 in tumors outside the colorectum has been previously reported. Moskaluk *et al*[12] and Werling *et al*[14] reported that a significant fraction of ovarian mucinous carcinomas and primary bladder adenocarcinomas were CDX2-positive and there have been other studies reporting CDX2 expression in adenocarcinomas of various anatomic sites.

CDX2 expression in cervical adenocarcinoma

Intestinal differentiation of cervical adenocarcinoma, in the form of goblet cells and/or Paneth cells, is uncommon but may generate diagnostic dilemmas. Invasive cervical adenocarcinomas with intestinal differentiation could mimic the histology of colorectal adenocarcinoma, raising the possibility of metastasis or direct spread. Also, a distant metastasis from an intestinal type cervical adenocarcinoma could be easily mistaken for a metastatic adenocarcinoma of an intestinal origin, based on morphology alone.

CDX2 immunostaining has been studied in a few large series of cervical adenocarcinomas of various histologic subtypes. McCluggage *et al*[52] have recently reported CDX2 positivity in the majority of intestinal-type endocervical adenocarcinomas *in situ* (20/21 cases) and in all the three invasive intestinal-type adenocarcinomas (ITAC) studied. We compared the expression of CDX2 in 119 cases of different types of cervical adenocarcinoma with that in rectal adenocarcinoma[53]. Our study is the largest reported to date and confirms that the majority of invasive and *in situ* endocervical adenocarcinomas of intestinal-type show CDX2 immunoreactivity[53], in agreement with the results of McCluggage *et al*[52] (Figure 1D).

CDX2 expression in primary ovarian mucinous tumors

Of all ovarian epithelial tumors, mucinous tumors pose the greatest difficulty with regard to differentiation between primary and metastatic tumors. Previous studies have demonstrated conflicting results regarding the value of CDX2 in distinguishing primary tumors from metastatic carcinomas of the ovary with mucinous morphology. CDX2 expression has been reported in from 0 to 100% of ovarian mucinous tumors and in 0% to 30% of ovarian endometrioid carcinomas[54-64]. In contrast, a recent study showed that almost all primary ovarian carcinomas lacked immunoreactivity for CDX2, while the majority of metastatic colorectal carcinomas of the ovary were CDX2-positive[57]. In an attempt to reconcile the wide gap in data from different studies, the authors claimed that previous studies may have misclassified ovarian metastases as primary tumors. Taken together, the results available to date suggest that the differential diagnosis of primary and metastatic mucinous carcinoma still poses a great problem because these tumors can share their immunophenotype, gross and microscopic features.

CDX2 expression in uterine endometrioid adenocarcinoma

Wani *et al*[65] investigated CDX2 expression in 225 cases of endometrial biopsies including 101 endometrioid carcinomas. Normal and non-proliferative endometrium showed negative CDX2 staining. Endometrioid carcinoma with squamous differentiation was positive for CDX2 in 73% of cases, whereas only 14% of tumors without squamous differentiation were positive (Figure 1E). In addition, the authors found that the larger the number of squamous foci the greater the number of CDX2 positive cells which correlated strongly with nuclear β-catenin expression. This may suggest an important role of CDX2 in squamous morular formation[65].

CDX2 expression in prostatic adenocarcinoma

Herawi *et al*[66] have investigated CDX2 expression in prostatic adenocarcinoma, including 708 tissue microarrays containing either benign or malignant prostate tissue as well normal tissues from various anatomic sites. Out of 185 prostatic adenocarcinomas, only four cases (6%) showed focal positive staining while benign prostatic tissue was positive in 12% of cases. No cases of metastatic prostatic carcinoma expressed CDX2[66]. Another study found CDX2 expression in 31% of prostatic adenocarcinoma with mucinous or signet cell differentiation[67]. However, in routine pathology practice, positive PSA immunostaining and clinical findings should prove more helpful when a prostatic origin is suspected for a metastatic adenocarcinoma[66,67].

CDX2 expression in urachal adenocarcinoma

The majority of urachal epithelial neoplasms are adenocarcinomas with enteric or nonenteric histologies. Urachal adenocarcinoma may mimic metastatic adenocarcinoma of different origins. Paner *et al*[68] studied CDX2 expression in 32 urachal adenocarcinomas and reported CDX2 expression in 85% of their cases. CDX2 expression can be diffuse in urachal adenocarcinomas, even without the classic enteric morphology. In urachal adenocarcinoma

subtypes, CDX2 expression was see in 8/8 (100%) of mucinous, 10/11 (91%) of enteric type, 5/7 (71%) of not otherwise specified, and in 4/6 (67%) of signet ring cell type. In addition, CDX2 was expressed by urachal remnants of glandular type, and noninvasive urachal mucinous cystic tumors[68].

CDX2 expression in intestinal-type sinonasal adenocarcinoma

ITAC of the nasal cavity and paranasal sinuses are uncommon[69]. They are clinically aggressive and generally present at an advanced stage. Franchi *et al*[69] demonstrated nuclear expression of CDX2 in all their cases of ITAC, with strong nuclear staining identified in the majority. CDX2 staining was not present in normal respiratory mucosa or seromucous glands. A similar study detected strong and diffuse nuclear expression of CDX2 in all cases of ITAC[70] (Figure 1F). Choi *et al*[71] suggested that the development of ITAC is preceded by intestinal metaplasia, with conversion from a normal CK7+/CK20-/CDX2-/villin- phenotype to an abnormal CK7-/CK20+/CDX2+/villin- intestinal phenotype.

CDX2 expression in acute myeloid leukemia

CDX2 is expressed in 90% of acute myeloid leukemia (AML) but not in hematopoietic stem and progenitor cells derived from normal individuals[72,73]. Frequent expression of CDX2 in the adult hematopoietic compartment suggests a role for CDX2 as part of a common effector pathway that promotes the proliferative capacity and self-renewal potential of myeloid progenitor cells[73].

CONCLUSION

CDX2 is a useful immunohistochemical marker for a colorectal origin of metastatic carcinoma. However, CDX2 can be expressed in other neoplasms, especially those with intestinal differentiation, irrespective of their origin. Therefore, CDX2 should not be used as the sole basis for the conclusion that the gastrointestinal tract is the primary origin of metastatic carcinomas. We recommend that CDX2 should always be used as a part of a broader immunohistochemical panel.

ACKNOWLEDGMENTS

We thank Pauline Henry, MD for her critical review of this article.

REFERENCES

1 **Beck F**. The role of Cdx genes in the mammalian gut. *Gut* 2004; **53**: 1394-1396
2 **Chawengsaksophak K**, James R, Hammond VE, Köntgen F, Beck F. Homeosis and intestinal tumours in Cdx2 mutant mice. *Nature* 1997; **386**: 84-87
3 **Eda A**, Osawa H, Yanaka I, Satoh K, Mutoh H, Kihira K, Sugano K. Expression of homeobox gene CDX2 precedes that of CDX1 during the progression of intestinal metaplasia. *J Gastroenterol* 2002; **37**: 94-100
4 **Mizoshita T**, Inada K, Tsukamoto T, Kodera Y, Yamamura Y, Hirai T, Kato T, Joh T, Itoh M, Tatematsu M. Expression of Cdx1 and Cdx2 mRNAs and relevance of this expression to differentiation in human gastrointestinal mucosa--with special emphasis on participation in intestinal metaplasia of the human stomach. *Gastric Cancer* 2001; **4**: 185-191
5 **Suh E**, Chen L, Taylor J, Traber PG. A homeodomain protein related to caudal regulates intestine-specific gene transcription. *Mol Cell Biol* 1994; **14**: 7340-7351
6 **Bai YQ**, Miyake S, Iwai T, Yuasa Y. CDX2, a homeobox transcription factor, upregulates transcription of the p21/WAF1/CIP1 gene. *Oncogene* 2003; **22**: 7942-7949
7 **Kaimaktchiev V**, Terracciano L, Tornillo L, Spichtin H, Stoios D, Bundi M, Korcheva V, Mirlacher M, Loda M, Sauter G, Corless CL. The homeobox intestinal differentiation factor CDX2 is selectively expressed in gastrointestinal adenocarcinomas. *Mod Pathol* 2004; **17**: 1392-1399
8 **Bonhomme C**, Duluc I, Martin E, Chawengsaksophak K, Chenard MP, Kedinger M, Beck F, Freund JN, Domon-Dell C. The Cdx2 homeobox gene has a tumour suppressor function in the distal colon in addition to a homeotic role during gut development. *Gut* 2003; **52**: 1465-1471
9 **Baba Y**, Nosho K, Shima K, Freed E, Irahara N, Philips J, Meyerhardt JA, Hornick JL, Shivdasani RA, Fuchs CS, Ogino S. Relationship of CDX2 loss with molecular features and prognosis in colorectal cancer. *Clin Cancer Res* 2009; **15**: 4665-4673
10 **Chung DC**. The genetic basis of colorectal cancer: insights into critical pathways of tumorigenesis. *Gastroenterology* 2000; **119**: 854-865
11 **Witek ME**, Nielsen K, Walters R, Hyslop T, Palazzo J, Schulz S, Waldman SA. The putative tumor suppressor Cdx2 is overexpressed by human colorectal adenocarcinomas. *Clin Cancer Res* 2005; **11**: 8549-8556
12 **Moskaluk CA**, Zhang H, Powell SM, Cerilli LA, Hampton GM, Frierson HF. Cdx2 protein expression in normal and malignant human tissues: an immunohistochemical survey using tissue microarrays. *Mod Pathol* 2003; **16**: 913-919
13 **De Lott LB**, Morrison C, Suster S, Cohn DE, Frankel WL. CDX2 is a useful marker of intestinal-type differentiation: a tissue microarray-based study of 629 tumors from various sites. *Arch Pathol Lab Med* 2005; **129**: 1100-1105
14 **Werling RW**, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol* 2003; **27**: 303-310
15 **Bakaris S**, Cetinkaya A, Ezberci F, Ekerbicer H. Expression of homeodomain protein CDX2 in colorectal adenoma and adenocarcinoma. *Histol Histopathol* 2008; **23**: 1043-1047
16 **Lugli A**, Tzankov A, Zlobec I, Terracciano LM. Differential diagnostic and functional role of the multi-marker phenotype CDX2/CK20/CK7 in colorectal cancer stratified by mismatch repair status. *Mod Pathol* 2008; **21**: 1403-1412
17 **Hinoi T**, Tani M, Lucas PC, Caca K, Dunn RL, Macri E, Loda M, Appelman HD, Cho KR, Fearon ER. Loss of CDX2 expression and microsatellite instability are prominent features of large cell minimally differentiated carcinomas of the colon. *Am J Pathol* 2001; **159**: 2239-2248
18 **Choi BJ**, Kim CJ, Cho YG, Song JH, Kim SY, Nam SW, Lee SH, Yoo NJ, Lee JY, Park WS. Altered expression of CDX2 in colorectal cancers. *APMIS* 2006; **114**: 50-54
19 **Saad RS**, Silverman JF, Khalifa MA, Rowsell C. CDX2, cytokeratins 7 and 20 immunoreactivity in rectal adenocarcinoma. *Appl Immunohistochem Mol Morphol* 2009; **17**: 196-201
20 **Groisman GM**, Amar M, Meir A. Expression of the intestinal marker Cdx2 in the columnar-lined esophagus with and without intestinal (Barrett's) metaplasia. *Mod Pathol* 2004; **17**: 1282-1288
21 **Kazumori H**, Ishihara S, Rumi MA, Kadowaki Y, Kinoshita

Y. Bile acids directly augment caudal related homeobox gene Cdx2 expression in oesophageal keratinocytes in Barrett's epithelium. *Gut* 2006; **55**: 16-25
22 **Lord RV**, Brabender J, Wickramasinghe K, DeMeester SR, Holscher A, Schneider PM, Danenberg PV, DeMeester TR. Increased CDX2 and decreased PITX1 homeobox gene expression in Barrett's esophagus and Barrett's-associated adenocarcinoma. *Surgery* 2005; **138**: 924-931
23 **Weimann A**, Zimmermann M, Gross M, Slevogt H, Rieger A, Morawietz L. CDX2 and LI-cadherin expression in esophageal mucosa: use of both markers can facilitate the histologic diagnosis of Barrett's esophagus and carcinoma. *Int J Surg Pathol* 2010; **18**: 330-337
24 **Bai YQ**, Yamamoto H, Akiyama Y, Tanaka H, Takizawa T, Koike M, Kenji Yagi O, Saitoh K, Takeshita K, Iwai T, Yuasa Y. Ectopic expression of homeodomain protein CDX2 in intestinal metaplasia and carcinomas of the stomach. *Cancer Lett* 2002; **176**: 47-55
25 **Park do Y**, Srivastava A, Kim GH, Mino-Kenudson M, Deshpande V, Zukerberg LR, Song GA, Lauwers GY. CDX2 expression in the intestinal-type gastric epithelial neoplasia: frequency and significance. *Mod Pathol* 2010; **23**: 54-61
26 **Mizoshita T**, Tsukamoto T, Nakanishi H, Inada K, Ogasawara N, Joh T, Itoh M, Yamamura Y, Tatematsu M. Expression of Cdx2 and the phenotype of advanced gastric cancers: relationship with prognosis. *J Cancer Res Clin Oncol* 2003; **129**: 727-734
27 **Almeida R**, Silva E, Santos-Silva F, Silberg DG, Wang J, De Bolós C, David L. Expression of intestine-specific transcription factors, CDX1 and CDX2, in intestinal metaplasia and gastric carcinomas. *J Pathol* 2003; **199**: 36-40
28 **Ge J**, Chen Z, Wu S, Yuan W, Hu B, Chen Z. A clinicopathological study on the expression of cadherin-17 and caudal-related homeobox transcription factor (CDX2) in human gastric carcinoma. *Clin Oncol* (R Coll Radiol) 2008; **20**: 275-283
29 **Shiotani A**, Kamada T, Yamanaka Y, Manabe N, Kusunoki H, Hata J, Haruma K. Sonic hedgehog and CDX2 expression in the stomach. *J Gastroenterol Hepatol* 2008; **23** Suppl 2: S161-S166
30 **Xin S**, Huixin C, Benchang S, Aiping B, Jinhui W, Xiaoyan L, Yu WB, Minhu C. Expression of Cdx2 and claudin-2 in the multistage tissue of gastric carcinogenesis. *Oncology* 2007; **73**: 357-365
31 **Kim HS**, Lee JS, Freund JN, Min KW, Lee JS, Kim W, Juhng SW, Park CS. CDX-2 homeobox gene expression in human gastric carcinoma and precursor lesions. *J Gastroenterol Hepatol* 2006; **21**: 438-442
32 **Liu Q**, Teh M, Ito K, Shah N, Ito Y, Yeoh KG. CDX2 expression is progressively decreased in human gastric intestinal metaplasia, dysplasia and cancer. *Mod Pathol* 2007; **20**: 1286-1297
33 **Song JH**, Kim CJ, Cho YG, Chae JS, Cao Z, Nam SW, Lee JY, Park WS. Genetic alterations of the Cdx2 gene in gastric cancer. *APMIS* 2008; **116**: 74-80
34 **Fan Z**, Li J, Dong B, Huang X. Expression of Cdx2 and hepatocyte antigen in gastric carcinoma: correlation with histologic type and implications for prognosis. *Clin Cancer Res* 2005; **11**: 6162-6170
35 **Seno H**, Oshima M, Taniguchi MA, Usami K, Ishikawa TO, Chiba T, Taketo MM. CDX2 expression in the stomach with intestinal metaplasia and intestinal-type cancer: Prognostic implications. *Int J Oncol* 2002; **21**: 769-774
36 **Okayama H**, Kumamoto K, Saitou K, Hayase S, Kofunato Y, Sato Y, Miyamoto K, Nakamura I, Ohki S, Sekikawa K, Takenoshita S. CD44v6, MMP-7 and nuclear Cdx2 are significant biomarkers for prediction of lymph node metastasis in primary gastric cancer. *Oncol Rep* 2009; **22**: 745-755
37 **Xie Y**, Li L, Wang X, Qin Y, Qian Q, Yuan X, Xiao Q. Overexpression of Cdx2 inhibits progression of gastric cancer in vitro. *Int J Oncol* 2010; **36**: 509-516
38 **Zhang MQ**, Lin F, Hui P, Chen ZM, Ritter JH, Wang HL. Expression of mucins, SIMA, villin, and CDX2 in small-intestinal adenocarcinoma. *Am J Clin Pathol* 2007; **128**: 808-816
39 **Wu XS**, Akiyama Y, Igari T, Kawamura T, Hiranuma S, Shibata T, Tsuruta K, Koike M, Arii S, Yuasa Y. Expression of homeodomain protein CDX2 in gallbladder carcinomas. *J Cancer Res Clin Oncol* 2005; **131**: 271-278
40 **Sakamoto H**, Mutoh H, Ido K, Satoh K, Hayakawa H, Sugano K. A close relationship between intestinal metaplasia and Cdx2 expression in human gallbladders with cholelithiasis. *Hum Pathol* 2007; **38**: 66-71
41 **Chang YT**, Hsu C, Jeng YM, Chang MC, Wei SC, Wong JM. Expression of the caudal-type homeodomain transcription factor CDX2 is related to clinical outcome in biliary tract carcinoma. *J Gastroenterol Hepatol* 2007; **22**: 389-394
42 **Hong SM**, Cho H, Moskaluk CA, Frierson HF, Yu E, Ro JY. CDX2 and MUC2 protein expression in extrahepatic bile duct carcinoma. *Am J Clin Pathol* 2005; **124**: 361-370
43 **Lin X**, Saad RS, Luckasevic TM, Silverman JF, Liu Y. Diagnostic value of CDX-2 and TTF-1 expressions in separating metastatic neuroendocrine neoplasms of unknown origin. *Appl Immunohistochem Mol Morphol* 2007; **15**: 407-414
44 **Srivastava A**, Hornick JL. Immunohistochemical staining for CDX-2, PDX-1, NESP-55, and TTF-1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors. *Am J Surg Pathol* 2009; **33**: 626-632
45 **Saqi A**, Alexis D, Remotti F, Bhagat G. Usefulness of CDX2 and TTF-1 in differentiating gastrointestinal from pulmonary carcinoids. *Am J Clin Pathol* 2005; **123**: 394-404
46 **Rabban JT**, Lerwill MF, McCluggage WG, Grenert JP, Zaloudek CJ. Primary ovarian carcinoid tumors may express CDX-2: a potential pitfall in distinction from metastatic intestinal carcinoid tumors involving the ovary. *Int J Gynecol Pathol* 2009; **28**: 41-48
47 **Saad RS**, Cho P, Silverman JF, Liu Y. Usefulness of Cdx2 in separating mucinous bronchioloalveolar adenocarcinoma of the lung from metastatic mucinous colorectal adenocarcinoma. *Am J Clin Pathol* 2004; **122**: 421-427
48 **Lora V**, Kanitakis J. CDX2 expression in cutaneous metastatic carcinomas and extramammary Paget's Disease. *Anticancer Res* 2009; **29**: 5033-5037
49 **Barbareschi M**, Murer B, Colby TV, Chilosi M, Macri E, Loda M, Doglioni C. CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. *Am J Surg Pathol* 2003; **27**: 141-149
50 **Saad RS**, Essig DL, Silverman JF, Liu Y. Diagnostic utility of CDX-2 expression in separating metastatic gastrointestinal adenocarcinoma from other metastatic adenocarcinoma in fine-needle aspiration cytology using cell blocks. *Cancer* 2004; **102**: 168-173
51 **Tot T**. Identifying colorectal metastases in liver biopsies: the novel CDX2 antibody is less specific than the cytokeratin 20+/7- phenotype. *Med Sci Monit* 2004; **10**: BR139-BR143
52 **McCluggage WG**, Shah R, Connolly LE, McBride HA. Intestinal-type cervical adenocarcinoma in situ and adenocarcinoma exhibit a partial enteric immunophenotype with consistent expression of CDX2. *Int J Gynecol Pathol* 2008; **27**: 92-100
53 **Saad RS**, Ismiil N, Dubé V, Nofech-Mozes S, Khalifa MA. CDX-2 expression is a common event in primary intestinal-type endocervical adenocarcinoma. *Am J Clin Pathol* 2009; **132**: 531-538
54 **Fraggetta F**, Pelosi G, Cafici A, Scollo P, Nuciforo P, Viale G. CDX2 immunoreactivity in primary and metastatic ovarian mucinous tumours. *Virchows Arch* 2003; **443**: 782-786
55 **Vang R**, Gown AM, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, Ronnett BM. Cytokeratins 7 and 20 in primary and secondary mucinous tumors of the ovary: analysis of coordinate immunohistochemical expression profiles and

staining distribution in 179 cases. *Am J Surg Pathol* 2006; **30**: 1130-1139
56 **Vang R**, Gown AM, Wu LS, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, Ronnett BM. Immunohistochemical expression of CDX2 in primary ovarian mucinous tumors and metastatic mucinous carcinomas involving the ovary: comparison with CK20 and correlation with coordinate expression of CK7. *Mod Pathol* 2006; **19**: 1421-1428
57 **Tornillo L**, Moch H, Diener PA, Lugli A, Singer G. CDX-2 immunostaining in primary and secondary ovarian carcinomas. *J Clin Pathol* 2004; **57**: 641-643
58 **Kim MJ**. The usefulness of CDX-2 for differentiating primary and metastatic ovarian carcinoma: an immunohistochemical study using a tissue microarray. *J Korean Med Sci* 2005; **20**: 643-648
59 **Logani S**, Oliva E, Arnell PM, Amin MB, Young RH. Use of novel immunohistochemical markers expressed in colonic adenocarcinoma to distinguish primary ovarian tumors from metastatic colorectal carcinoma. *Mod Pathol* 2005; **18**: 19-25
60 **Lagendijk JH**, Mullink H, Van Diest PJ, Meijer GA, Meijer CJ. Tracing the origin of adenocarcinomas with unknown primary using immunohistochemistry: differential diagnosis between colonic and ovarian carcinomas as primary sites. *Hum Pathol* 1998; **29**: 491-497
61 **McCluggage WG**. Recent advances in immunohistochemistry in the diagnosis of ovarian neoplasms. *J Clin Pathol* 2000; **53**: 327-334
62 **Groisman GM**, Meir A, Sabo E. The value of Cdx2 immunostaining in differentiating primary ovarian carcinomas from colonic carcinomas metastatic to the ovaries. *Int J Gynecol Pathol* 2004; **23**: 52-57
63 **Lagendijk JH**, Mullink H, van Diest PJ, Meijer GA, Meijer CJ. Immunohistochemical differentiation between primary adenocarcinomas of the ovary and ovarian metastases of colonic and breast origin. Comparison between a statistical and an intuitive approach. *J Clin Pathol* 1999; **52**: 283-290
64 **Raspollini MR**, Amunni G, Villanucci A, Baroni G, Taddei A, Taddei GL. Utility of CDX-2 in distinguishing between primary and secondary (intestinal) mucinous ovarian carcinoma: an immunohistochemical comparison of 43 cases. *Appl Immunohistochem Mol Morphol* 2004; **12**: 127-131
65 **Wani Y**, Notohara K, Saegusa M, Tsukayama C. Aberrant Cdx2 expression in endometrial lesions with squamous differentiation: important role of Cdx2 in squamous morula formation. *Hum Pathol* 2008; **39**: 1072-1079
66 **Herawi M**, De Marzo AM, Kristiansen G, Epstein JI. Expression of CDX2 in benign tissue and adenocarcinoma of the prostate. *Hum Pathol* 2007; **38**: 72-78
67 **Leite KR**, Mitteldorf CA, Srougi M, Dall'oglio MF, Antunes AA, Pontes J, Camara-Lopes LH. Cdx2, cytokeratin 20, thyroid transcription factor 1, and prostate-specific antigen expression in unusual subtypes of prostate cancer. *Ann Diagn Pathol* 2008; **12**: 260-266
68 **Paner GP**, McKenney JK, Barkan GA, Yao JL, Frankel WL, Sebo TJ, Shen SS, Jimenez RE. Immunohistochemical analysis in a morphologic spectrum of urachal epithelial neoplasms: diagnostic implications and pitfalls. *Am J Surg Pathol* 2011; **35**: 787-798
69 **Franchi A**, Massi D, Palomba A, Biancalani M, Santucci M. CDX-2, cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinomas of the sinonasal tract. *Virchows Arch* 2004; **445**: 63-67
70 **Kennedy MT**, Jordan RC, Berean KW, Perez-Ordoñez B. Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma. *J Clin Pathol* 2004; **57**: 932-937
71 **Choi HR**, Sturgis EM, Rashid A, DeMonte F, Luna MA, Batsakis JG, El-Naggar AK. Sinonasal adenocarcinoma: evidence for histogenetic divergence of the enteric and nonenteric phenotypes. *Hum Pathol* 2003; **34**: 1101-1107
72 **Riedt T**, Ebinger M, Salih HR, Tomiuk J, Handgretinger R, Kanz L, Grünebach F, Lengerke C. Aberrant expression of the homeobox gene CDX2 in pediatric acute lymphoblastic leukemia. *Blood* 2009; **113**: 4049-4051
73 **Thoene S**, Rawat VP, Heilmeier B, Hoster E, Metzeler KH, Herold T, Hiddemann W, Gökbuget N, Hoelzer D, Bohlander SK, Feuring-Buske M, Buske C. The homeobox gene CDX2 is aberrantly expressed and associated with an inferior prognosis in patients with acute lymphoblastic leukemia. *Leukemia* 2009; **23**: 649-655

S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v3.i11.167

World J Gastrointest Surg 2011 November 27; 3(11): 167-176
ISSN 1948-9366 (online)

REVIEW

Current status and recent advances of liver transplantation from donation after cardiac death

M Thamara PR Perera, Simon R Bramhall

M Thamara PR Perera, Simon R Bramhall, The Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, United Kingdom

Author contributions: Perera MTPR designed the the study, collected, analyzed and made the interpretation of the data, and drafted the article; Bramhall SR designed the conception, revised the manuscript critically for important intellectual content, and made the final approval of the version to be published.

Correspondence to: Mr. Simon R Bramhall, Consultant HPB and Transplant Surgeon, The Liver Unit, Queen Elizabeth Hospital, Nuffield House 3rd Floor, Edgbaston, Birmingham B15 2TH, United Kingdom. simon.bramhall@uhb.nhs.uk
Telephone: +44-121-6272346 Fax: +44-121-4141833
Received: July 30, 2011 Revised: October 21, 2011
Accepted: October 28, 2011
Published online: November 27, 2011

Abstract

The last decade saw increased organ donation activity from donors after cardiac death (DCD). This contributed to a significant proportion of transplant activity. Despite certain drawbacks, liver transplantation from DCD donors continues to supplement the donor pool on the backdrop of a severe organ shortage. Understanding the pathophysiology has provided the basis for modulation of DCD organs that has been proven to be effective outside liver transplantation but remains experimental in liver transplantation models. Research continues on how best to further increase the utility of DCD grafts. Most of the work has been carried out exploring the use of organ preservation using machine assisted perfusion. Both *ex-situ* and *in-situ* organ perfusion systems are tested in the liver transplantation setting with promising results. Additional techniques involved pharmacological manipulation of the donor, graft and the recipient. Ethical barriers and end-of-life care pathways are obstacles to widespread clinical application of some of the recent advances to practice. It is likely that some of the DCD offers are in fact probably "prematurely" offered without ideal donor management or even prior to brain death being established. The absolute benefits of DCD exist only if this form of donation supplements the existing deceased donor pool; hence, it is worthwhile revisiting organ donation process enabling us to identify counter remedial measures.

Key words: Non-heart beating donor; Liver graft; Primary non-function; Reperfusion injury; Modulation

Peer reviewer: Uwe Klinge, MD, Professor, Institute for Applied Medical Engineering AME, Helmholtz Institute, RWTH Aachen Pauwelsstrabe 30, Aachen 52074, Germany

Perera MTPR, Bramhall SR. Current status and recent advances of liver transplantation from donation after cardiac death. *World J Gastrointest Surg* 2011; 3(11): 167-176 Available from: URL: http://www.wjgnet.com/1948-9366/full/v3/i11/167.htm DOI: http://dx.doi.org/10.4240/wjgs.v3.i11.167

INTRODUCTION

The current literature suggests that outcomes of liver transplantation using organs from donors after cardiac death (DCD) are nearly comparable to that of donors after brain death (DBD) or live donor transplants[1-3]. However, these results are obtained at the expense of significant peri-operative and long term morbidity to the recipient and add substantial cost to the health economics. In countries where transplant programs depend on deceased donors for the supply of organs, there appears to be a recent increase in DCD numbers. In the United Kingdom alone, DCD activity contributed up to 35% of deceased donor transplants in the year 2009-2010. The United Network for Organ Sharing (UNOS) data suggests similar trends, with DCD accounting up to 10% of

overall transplant activity. The initial euphoria of DCD as a viable and alternative organ source is diminishing with the realisation that these DCD organs have contributed to an increased number of transplants at the expense of DBD organs (Figure 1).

There is a lack of universally acceptable objective criteria in identification of an ideal DCD donor and suitable recipient selection. With ever growing transplant waiting lists and death while on the list, clinicians are always on the lookout for means of pushing the boundaries; which donors can be accepted for DCD donation and which organs can be safely transplanted into which potential recipient. The big unanswered question that remains is "which potential DCD donor would become a DBD donor if appropriately managed?" but this is beyond the control of transplant surgeons and lies in the hands of the intensivists who manage most of these donors prior to the referral[4,5].

Translational studies are not readily incorporated in to the practice in the field of DCD liver transplantation. The bulk of the evidence on clinical outcomes consists of retrospective and observational series. On a positive note, there is evidence on manipulation of DCD grafts, potentially rectifying initial warm ischemia induced organ injury[6]. Most of the problems associated with DCD liver transplantation are related to the additional ischemic insult that occurs following cardiac death and until organ perfusion with preservation solution is commenced. The exaggerated ischemia reperfusion injury might be potentially life threatening to the recipient upon reperfusion of the graft[7]. A higher incidence of significant organ dysfunction, delayed graft function with primary non-function is reported with organs from DCD donors[8,9]. Dependency on organ support in the immediate post operative period is an added burden on healthcare systems, in addition to increased risk of long term complications e.g. biliary complications in DCD liver grafts.

In this review we aim to analyze the current literature on outcomes, results and complications of DCD liver transplantation and investigate interventional and experimental strategies to overcome issues related to DCD liver transplantation.

HISTORICAL PERSPECTIVES

For many years, liver transplant programs, based on deceased organ donation programs, have depended on "cadaveric donors" where death has been confirmed by brain stem death testing. These donors are called heart beating donors but more recently have become known as deceased after brain death (DBD) donors. Liver transplantation became an accepted treatment for end stage liver disease following the refinement of immunosuppression therapy that resulted in improved long term graft and patient survival. The increasing success of liver transplantation led to a widening of the indications and in the UK was at a time of a reduction in the number of potential donors offered to the donor coordinator

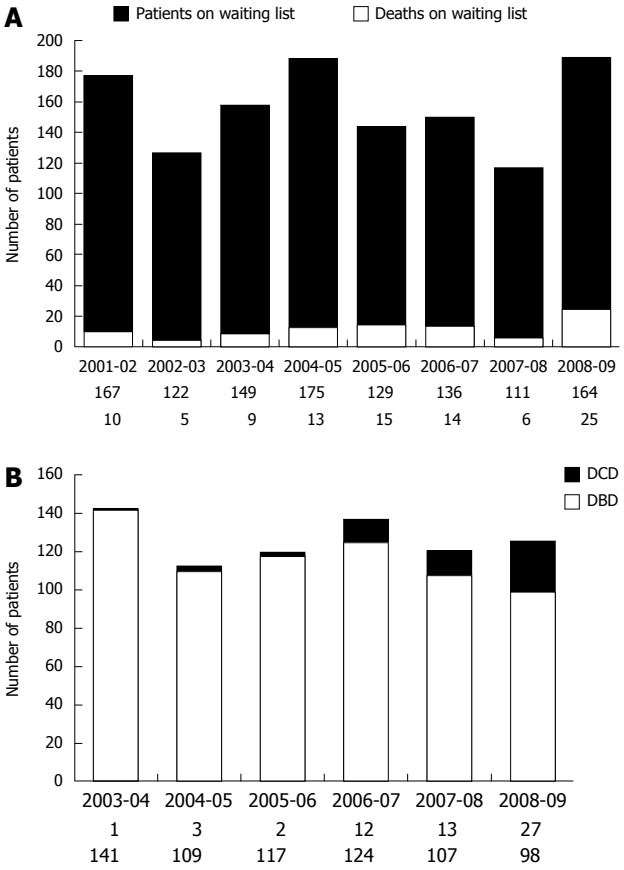


Figure 1 Data from the Queen Elizabeth Hospital Birmingham Liver Transplant Unit. (A) Note the average number of patients in the transplant wait list, especially in the years 2001/02, 2004/05 and 2008/09 had not changed; in contrast, the mortality while on transplant wait list has been significantly increased despite an increase in the LT activity from donors after cardiac death donors (B).

teams to a point where the organ supply did not meet the demand, and so surgeons explored alternative organ sources.

The concept of non-heart beating donation or donation after cardiac death (DCD) was re-visited as a viable source of liver grafts in this setting[10]. DCD donation was in fact not a new phenomenon but could be regarded as a revival of a historical procedure first performed in 1933. Historically, almost all renal transplants were carried out using DCD organs following the first published report in 1955[11]. There was a revival of DCD activity towards the end of the 20th Century[12-14]; this success in the light of a reducing pool of DBD donors prompted liver transplant surgeons to re-explore the possibility of grafts from DCD donors for liver transplantation[15-18]. In the 1990s, there was increased activity of DCD liver transplantation in the United States and Europe, which led to the 1st DCD conference held in 1995[19,20]. During this conference, experts gathered in Maastricht defined the categories of DCD donors, widely known as Maastricht criteria. The following four categories were defined: Category Ⅰ - Death on arrival; Category Ⅱ - Failed resuscitation; Category Ⅲ - Awaiting cardiac arrest, generally

comprising planned withdrawal of life support of an in-hospital (ITU) patient; Category Ⅳ - Cardiac arrest after brain stem death.

Categories Ⅰ and Ⅱ are known as "uncontrolled" donors owing to lack of the time of cardiac arrest; hence the predictability of initial warm ischemia. In contrast, types Ⅲ/Ⅳ donors have a more predictable course before the cardiac death and were termed "controlled" donors. The outcomes of livers from uncontrolled DCD donors were poor; only a few reports have been published on liver transplantation using these donors and some form of cardio-pulmonary support was employed in these donors to maintain recirculation[8,21]. Substantial data on renal transplantation from uncontrolled DCD donors exists; however, most liver transplant programs only use controlled DCD donors at present[22]. Initial results following controlled DCD transplantation were acceptable and similar to that of livers from DBD donors; initially this donor organ source was thought to be a supplement to reducing numbers of organs from DBD donor sources.

CURRENT TREND IN DCD DONATION

In the UK, DCD donation activity has increased by 100% over the last few years. One would expect this to have contributed to a parallel increase in the overall transplant activity, but in reality, the total number of deceased donors (DCD and DBD) and the number transplants has remained static or declined in comparison to the previous years. Therefore, it appears that the DCD activity has increased at the expense of DBD activity. We speculate that this might be explained by some DCD donors being referred prior to the establishment of brain stem death. This is opposite to UNOS data which suggests that DCD activity has increased to supplement the overall transplant activity[16].

PATHOPHYSIOLOGY OF DCD

Following withdrawal of treatment in DCD donors, organs suffer an ischemic insult resulting from hypotension and desaturation below the levels that are required to maintain adequate tissue perfusion. In our own unit, we consider blood pressure < 50 mmHg and oxygen saturation < 80% as heralding the beginning of warm ischemia. Intracellular energy charge is paramount for cellular viability[23,24]. In the absence of oxygenated perfusion during warm ischemia, anaerobic metabolism heralds intracellular energy depletion, lactic acidosis and paralysis of energy driven Na^+/K^+ pumps that maintain cell membrane integrity culminating in edema, intracellular vacuolation and cell death. In general, it is accepted that hepatocytes withstand sustained warm ischemic injury for up to 30 min, and grafts transplanted beyond this limit have a higher incidence of primary non function[25]. The degree of intracellular vacuolation has been shown to be predictive of the eventual graft outcome in pig liver transplantation[26], although this is not routinely examined in the clinical setting.

Another factor which is detrimental to DCD grafts is post-mortem clot formation in the hepatic microvasculature. This leads to differential and non-uniform perfusion during both organ retrieval and upon reperfusion and eventually determines subsequent graft function. Additional problems specific to liver transplantation include biliary epithelial damage leading to ischemic type biliary strictures (ITBL)[21]. Bile ducts derive an exclusive arterial blood supply and poor perfusion of the biliary microvasculature is implicated in ITBL. The incidence of biliary strictures is also associated with inadequate bile duct flush at the commencement of cold ischemia. Inspissated bile salts are deposited inside the intrahepatic segmental ducts causing biliary epithelial injury progressing to strictures[27].

The added ischemic insult in DCD grafts compared with DBD donor grafts can provoke severe ischemia reperfusion injury after transplantation. This can lead to cardiovascular, renal and systemic instability and oxygen derived free radicals are implicated[28]. Various biomarkers have been described to quantify the ischemic injury prior to organ retrieval or transplantation, with the objective of assessing suitability of grafts for transplantation; these include xanthine, hypoxanthine, hyaluronic acid and reduced glutathione *etc*.[29-33]. Hypoxanthine is a catabolic by-product of intracellular ATP depletion and upon reperfusion with oxygenated blood becomes oxidised to xanthine. Both molecules possess the potential to generate free radicals which are implicated in ischemia reperfusion injury[28,34]. Proportionate increase in extracellular hypoxanthine was shown to be associated with duration warm ischemia reflecting increased free radical production, poor graft viability and function[31]. Undoubtedly, assessment of these biomarkers in DCD liver grafts prior to implantation would be helpful. Certain technical limitations, namely the failure to identify these biomarkers in the peripheral body fluids, technical demands and time constraints in the actual clinical setting, preclude them from being incorporated in to current practice.

CLINICAL OUTCOMES OF DCD

The incidence of delayed graft function and primary non-function is higher in livers from DCD donors and this leads to patient instability in the early post transplant period. Worsening liver function tests in the presence of acidosis and coagulopathy are poor prognostic markers. The reported incidence of primary non-function is up to 15% following transplantation of a DCD donor liver[21,35]. This is 4-5 fold higher when compared to livers from DBD donors. The risk of PNF further increases with prolongation of the cold ischemia time[36]. Some authors have suggested that cold ischemia is more detrimental to DCD grafts[37].

The early results of graft and patient survival following liver transplantation from DCD donors were comparable to that of transplantation from DBD donors[38]. Refinements of donor procurement, preservation, donor

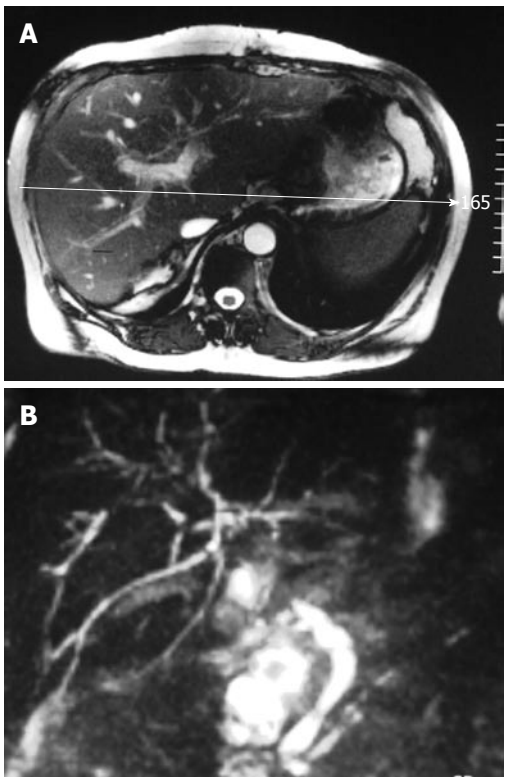


Figure 2 Magnetic resonance cholangiopancreatography images of 60-year-old patient received a donors after cardiac death liver graft received 7 years ago. Patient developed ischemic type intrahepatic biliary strictures 8 mo since transplant, confirmed to be of ischemic origin by liver biopsy. Note: dilated intrahepatic ducts proximal to intrahepatic biliary strictures.

organ selection and peri-operative care has resulted in improved outcomes in the last decade. At present, the long term patient and graft survival stands at 60%-70% at 5 years following liver transplantation from a DCD donor. A recent report even suggested equal survival outcomes[1]. Strict donor selection criteria probably contributed to these results that may not be possible to apply in most of the other centers[39].

ITBL is associated with long term morbidity and risk of further surgical and non-surgical interventions and even re-transplantation[35,40]. Isolated intrahepatic lesions may have an indolent course in the presence of free biliary drainage from the unaffected hepatic parenchyma (Figure 2). Involvement of major bile ducts or the extrahepatic biliary system, however, is not uncommon and warrants aggressive management[41]. The risk of ITBL appears extremely high and is reported in up to 50% of uncontrolled DCD transplantation[21]. Although less frequent, in the controlled DCD setting the highest reported incidence is between 30%-40%[40,42].

Anecdotal evidence suggests that there is a tendency for an increased use of hospital resources, including intensive care facilities, renal support including dialysis and hemofiltration during the early post transplant period in those recipients receiving a DCD donor liver when compared with those receiving a DBD donor liver. There is no published evidence to support this theory; however, some initial unpublished work that has been carried out in our institution points towards such trend. This means increased financial costs associated with DCD donation and the recipients are at greater operative risk.

Despite all of these shortcomings, DCD donor grafts have been able to save lives of patients with both acute and chronic liver failure and have been used as either full or segmental grafts[43,44]. Despite the substantial risk carried with such procedures, the long term outcomes have been satisfactory. Based on these limited data, it could be speculated that these grafts may even be routinely used in the setting of acute liver failure for emergency transplants or used as split grafts benefiting two recipients[45,46]. The key to success is careful donor selection when DCD donor grafts are considered for such extreme clinical situations.

CURRENT RESEARCH

There are a number of levels of intervention that offer potential areas of research on reconditioning of DCD liver grafts (Figure 3). Most of the published studies are in animals and a significant proportion of these included surrogate biomarker analysis in non-transplant models. How these data extrapolate to clinical practice remains unclear. In countries where DCD transplantation (mostly renal transplants) from category II donors is practiced, some of these techniques have been employed in the clinical setting with better long term outcomes for the recipients and grafts[12]. Reconditioning of non heart beating donors offers an opportunity to both improve outcomes and increase the availability of DCD donor organs. Understanding the pathophysiology of DCD donation has enabled many investigators to explore the impact of pharmacological manipulation and both *in-situ* and *ex-situ* machine perfusion has begun to become a real clinical possibility. The success of *ex-situ* machine perfusion of kidney grafts from DCD donors[12,47-49] has been begun to be adapted by other specialties, including cardiac transplantation[50].

Numerous methods of improving the quality of the DCD grafts have been described and the different terminology adds to confusion. The two principle techniques of machine perfusion described are "hypothermic" and "normothermic". During hypothermic perfusion, graft energy stores are replenished whilst normothermic reperfusion goes a step further and is aimed at reviving DCD grafts from ischemic injury. Depending on the timing of application, such procedures are further classified as "pre-conditioning" and "post-conditioning". Apart from machine perfusion, these terms may also encompass other pharmacological modulation/intervention of grafts. Pre-conditioning refers to such applications carried out at the time of retrieval or after the retrieval but prior to cold storage of organs. In contrast, post-conditioning refers to techniques that are employed after cold storage and immediately prior to the reperfusion in the recipient.

Extra-corporeal (ex-vivo) perfusion

The Oxford Group studied the benefits of normother-

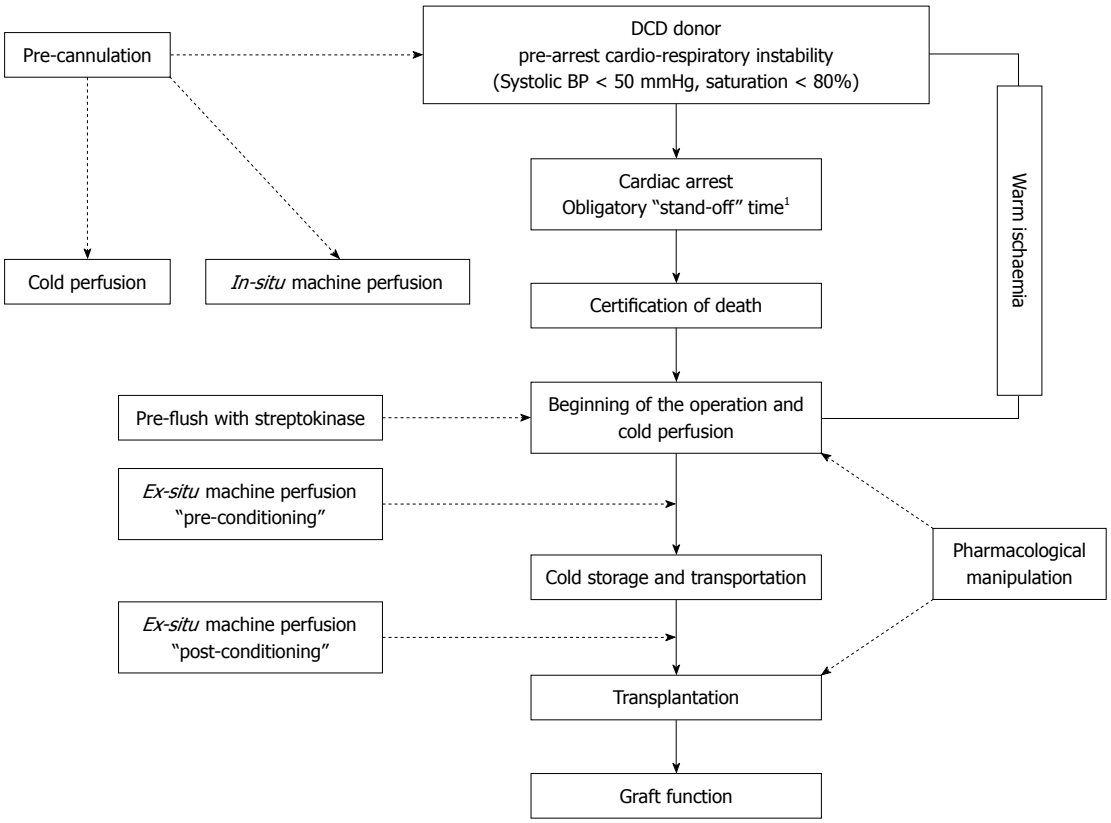


Figure 3 Diagrammatic representation of major steps in donors after cardiac death donation and current research targets. [1]Obligatory stand-off time varies according to the setting; in the United Kingdom this is 5 min whilst 2-10 min are being observed by others according to the centre policy. DCD: Donors after cardiac death.

mic machine perfusion extensively. Imber *et al*[51,52] (2002) reported that normothermic perfusion is superior to the traditional UW solution based cold storage. Total extracorporeal machine perfusion has its disadvantages owing to technical difficulties in vascular connections; expertise and organ transport, *etc*., and hence may not be practical in most situations. Subsequently Reddy *et al*[53] (2004) explored the possibility of post-conditioning of liver grafts that have been stored in the cold storage for a limited period. This model has more practical sense as in real practice the organs could be transported (cold stored) to the recipient center and "post-conditioned" with normothermic perfusion for a certain period of time prior to implantation. The authors concluded that sequential cold storage followed by normothermic perfusion is detrimental to the grafts, leading to more hepatocyte injury. Subsequent to this, the same group tested a similar model but with shorter cold ischemia compared to their previous study, and they demonstrated that hepatocytes retained the synthetic function after brief cold ischemia and more prolonged post conditioning[37]. The results from Gong *et al*[54] (2008) had also drawn similar conclusions following normothermic perfusion of swine liver when compared to cold stored liver in histidine-tryptophan-ketogluterate solution.

The results of hypothermic perfusion appear to be different to that of normothermic models. Several studies have suggested post conditioning in the experimental liver transplant as well as renal transplant setting where hypothermic post conditioning yielded better outcomes[55-57]. Extra-corporeal oxygenated machine perfusion (ECMO) of DCD liver grafts was shown to be superior to the traditionally cold stored liver grafts[58]. The key elements of hypoxia induced cellular injury are shown to be reversible in pre-conditioned grafts perfused with oxygenated buffer using the extracorporeal perfusion system[59]. Short term hypothermic oxygenated machine perfusion restored intracellular ATP and gave better post-transplant biochemical parameters than those transplanted without such intervention[58]. Work carried out by Manekeller *et al*[60] (2007) reported comparable outcomes in terms of bile acid production, ammonia clearance, vascular resistance and oxygen utilisation of DCD liver grafts treated with a short period of post conditioning prior to viability assessment. The authors concluded that prolonged cold ischemia may potentially augment injury caused by warm ischemia; some of the conclusions drawn in this study may be considered speculative in the presence of drawbacks in their study design[60] (Table 1).

Machine perfusion alone, however, may not provide the solutions to the problems associated with DCD livers. Jain *et al*[61] (2004) extensively studied the hemodynamic perfusion changes occurring during hypothermic perfusion at extremes of cold ischemia time extending to 24 h. Such long cold ischemia is not expected in the routine clinical setting but some of their observations highlight

Table 1 Summary data on normothermic *ex-vivo* perfusion studies of donors after cardiac death liver

Author	Yr	Model	Summary	Outcome
Gong *et al*[54]	2008	Animal (swine)	Normothermic perfusion with autologous blood (n = 4), compared with cold stored controls in HTK solution (n = 4)	Improved bile production, less hepatocyte damage and favourable haemodynamic parameters
Manekeller *et al*[60]	2007	Animal (rat)	Oxygenated hypothermic machine perfusion at the end of cold storage (post perfusion)	Improved performance indicators comparable to controls
Reddy *et al*[37]	2005	Animal (swine)	Normothermic perfusion for 24 h (n = 5%) compared with sequential cold storage of 1 h followed by 20 h normothermic perfusion (n = 5)	Greater hepatocyte injury whilst retaining the synthetic function
Reddy *et al*[53]	2004	Animal (swine)	Normothermic perfusion for 24 h (n = 4) compared with sequential 4 h cold storage followed by 20 h normothermic reperfusion (post-conditioning, n = 4)	Greater hepatocyte injury in the sequential post conditioning group
St Peter *et al*[55]	2002	Animal (swine)	Hypothermic storage (n = 4) compared to normothermic perfusion *ex-vivo* (n = 4) - reperfusion model not transplant	Recovery of synthetic function, less hepatocyte injury and improved substrate utilisation
Imber *et al*[51]	2002	Animal (swine)	Normothermic perfusion (n = 5) compared with standard cold storage (n = 5)	Improved bile production, glucose metabolism and less hepatocyte injury

HTK: Histidine-tryptophan-ketoglutarate.

the problems peculiar to DCD livers. It was shown that heterogenous microvascular perfusion occurred with hypothermic perfusion, probably resulting from endothelial cell injury. This has been confirmed by other studies[25]; a similar heterogenous perfusion is commonly observed in the clinical setting that is directly associated with perioperative instability of recipient and reflected on subsequent graft dysfunction.

In-vivo (in-situ) perfusion

A novel approach is the "*in-situ* (*vivo*)" machine perfusion and current interest is centred on *in-situ* perfusion using autologous blood and an ECMO device. This obviates the need for exhaustive techniques to reconnect the organs to the machine; hence, appears simple when the technical aspects alone are compared with its counterpart "*ex-situ* (*vivo*)" machine perfusion. The first results of *in-situ* perfusion with an ECMO device was published by Ko *et al*[62] (2000); the authors reported of the use of an ECMO assisted perfusion when legal barriers precluded organ retrieval from DCD donors after certification of cardiac death. The group published data on 8 renal transplants performed after reviving the organs with hypothermic circulation driven by ECMO and reported immediate graft function in 75% cases, whilst delayed graft function was observed in the remainder. This group reproduced similar results in a subsequent publication which created an interest in the *in-vivo* revival of DCD organs[63].

Quintela *et al*[64] (2005) reported the earliest clinical results of liver transplantation from a technique that could be simulated to autologous re-perfusion and without a mechanical device; the importance is that this is the only reported clinical series and the donors in this series could be regarded type Ⅱ DCD donors. They reported 10 liver transplants performed using grafts that were maintained by abdominal compression-decompression to maintain organ perfusion. Successful results reported by this group have not been reproduced by the same or any other groups to date.

There is very limited data on the performance of liver grafts that have been perfused *in-situ* with normothermic perfusion techniques. Rojas *et al*[65] (2004) reported their results on swine maintained on ECMO following induced cardiac arrest, and concluded venous oxygen saturation reached the baseline pre-cardiac arrest levels within 15 min of ECMO perfusion, whilst retaining 75% of synthetic function following warm ischemia. These results are exciting, but no other groups have reported similar results. The same group recently published data on a similar model with 30 min of induced warm ischemia followed by ECMO support[66]. Organs were recovered to a transplantable level. The prospects of *in-vivo* perfusion appear sound as technical aspects are less cumbersome when compared to extracorporeal perfusion techniques. A major obstacle is application of such a technique to human model and overcoming the ethical and legal barriers.

Pharmacological agents and modulation

The initial reports of pre-flush with streptokinase were centered on renal transplantation demonstrating the improved microvascular permeability and graft function[67,68]. The convincing results led to routine incorporation of this to the practice among many centers[69]. In the DCD liver grafts of an *ex-vivo* transplant model, heterogenous patchy perfusion resulting in loss of cellular integrity had been shown when not treated with anti-fibrinolytic streptokinase solution[70]. Yamauchi *et al*[71] (2000) reported improved microvascular perfusion in the rat liver transplantation model using DCD grafts pre-flushed with streptokinase.

Multifactorial "modulation" of DCD donors with the use of pharmacological agents was reported in a recent animal study[6]. The investigators used a combined pharmacological modulation "*in-situ*" as well as during the recipient operation. The agents used mainly were antithrombogeneic and vasodilatatory (streptokinase, heparin, epoprostenol) and biological agents (primarily redox

agents) aiming to minimise the ischemia reperfusion injury[6,72]. The livers were exposed to 45 min of warm ischemia, followed by a cold storage prior to transplant. The investigators reported a lower incidence of primary non-function, improved hepatic synthetic activity and less parenchymal loss following modulation. They also reported lower bile salt-to-phospholipid ratio in the modulation group. Increased bile salt-to-phospholipid ratio has been previously attributed by the same investigators for the higher incidence of ITBL[27]. The protective effect of L-arginine in relation to attenuation of nitric oxide and plasma endothelin release has also been reported[73]. It appears that scientists have made some headway in addressing key issues related to DCD liver transplantation; however, these are yet to be proven by long term follow up studies and application to clinical practice.

FUTURE OF DCD LIVER TRANSPLANTATION

The lack of a universally accepted and safe criterion for age of the donor and the amount of macro- and microvesicular steatosis in the setting of DCD liver grafts remains a problem. Investigators have so far been looking only at the revival of warm ischemic damage, but other surrogate factors should be investigated in the context of initial poor function. Primary non function donor-recipient matching is inevitably carried out at present and tends to be based on clinical and performance indicators in both the donor and recipient; however, models are needed that score the risk of DCD grafts taking other parameters in to account[74]. This would help identify the best recipient for a particular DCD or DBD graft[7]. This would ensure that organ wastage from discard and recipient complications would be minimised.

Judging by the current popularity, it may be speculated that in the future, DCD liver transplantation will contribute a significant proportion of the liver transplant activity. Whether this increased activity of DCD donation is the end results of the organ donation process through awareness among both public and medical personnel alike, or increased DCD activity at the expense of DBD activity, remains in question. Pressure for ITU beds may prompt intensivists to withdraw life support at the earliest opportunity when it is evident that further treatment of a patient is futile. It is known that the majority of patients with intra-cerebral pathologies are managed with a relatively dry fluid regime in order to prevent intracerebral edema; meanwhile, donor optimisation prior to organ retrieval involves fluid, electrolytes, blood sugar and hormonal support and prevention of infection[75,76]. It is likely that if these patients with intra-cerebral pathology were managed using the optimisation guidelines then a proportion would become brain dead within the next few hours[77].

In our experience, there have been many instances where DCD donor offers were converted to DBD offers at the last minute, even just prior to commencement of organ retrieval. As discussed above, experience suggests that, with further management for a few hours, even more DCD offers would almost certainly see the donors become brain dead[78]. Ethical or legal barriers may preclude pharmacological or other manipulation of the donor in some countries. In the United Kingdom, amendments to the Human Tissue Act introduced recently declared that once a suitable recipient has been identified to receive organs from a potential donor, the organs belong to the recipient. This amendment might allow us to challenge critics who suggest donor management/manipulation to optimise organ donation is legally and ethically flawed once it is decided that further treatment is futile[79]. Liver transplantation with DCD organs should also be looked upon as a life saving operation; it is important that every professional involved from donor care to transplantation realises that the price a recipient will have to pay is higher when receiving DCD donor organs than a DBD graft[80].

The revival of donor liver organs is yet to be translated to clinical practice. Unlike in renal transplantation where one can take a calculated risk and if unsuccessful return to dialysis, liver transplantation using these manipulated livers is a very big risk. What has been achieved so far is promising and combined pharmacological manipulation and ECMO support appears the way forward. *In-situ* revival appears a better option. In the future, we could see a transition from animal to human models at least at the pre-transplant level. In view of the increased demand for donor livers, it is likely that progress made on the issues discussed would increase DCD liver transplantation, contributing to a true and meaningful rise in overall transplant activity.

REFERENCES

1 **Dubbeld J**, Hoekstra H, Farid W, Ringers J, Porte RJ, Metselaar HJ, Baranski AG, Kazemier G, van den Berg AP, van Hoek B. Similar liver transplantation survival with selected cardiac death donors and brain death donors. *Br J Surg* 2010; **97**: 744-753

2 **Fujita S**, Mizuno S, Fujikawa T, Reed AI, Kim RD, Howard RJ, Hemming AW. Liver transplantation from donation after cardiac death: a single center experience. *Transplantation* 2007; **84**: 46-49

3 **Manzarbeitia CY**, Ortiz JA, Jeon H, Rothstein KD, Martinez O, Araya VR, Munoz SJ, Reich DJ. Long-term outcome of controlled, non-heart-beating donor liver transplantation. *Transplantation* 2004; **78**: 211-215

4 **Gardiner D**, Sparrow R. Not dead yet: controlled non-heart-beating organ donation, consent, and the Dead Donor Rule. *Camb Q Healthc Ethics* 2010; **19**: 17-26

5 **Griffiths J**, Verble M, Falvey S, Bell S, Logan L, Morgan K, Wellington F. Culture change initiatives in the procurement of organs in the United kingdom. *Transplant Proc* 2009; **41**: 1459-1462

6 **Monbaliu D**, Vekemans K, Hoekstra H, Vaahtera L, Libbrecht L, Derveaux K, Parkkinen J, Liu Q, Heedfeld V, Wylin T, Deckx H, Zeegers M, Balligand E, Buurman W, van Pelt J, Porte RJ, Pirenne J. Multifactorial biological modulation of warm ischemia reperfusion injury in liver transplantation from non-heart-beating donors eliminates primary non-function and reduces bile salt toxicity. *Ann Surg* 2009; **250**: 808-817

7 **Dezza MC**, Berrevoet F, Sainz-Barriga M, Rossetto A, Colen-

bie L, Haentjens I, Van Vlierberghe H, Colle I, Van Huysse J, Praet M, Rogiers X, de Hemptinne B, Troisi R. The choice of recipient does not have a bearing on early outcome in liver transplant patients receiving grafts from non-heart-beating donors: a reappraisal? *Transplant Proc* 2007; **39**: 2675-2677

8 **Otero A**, Gómez-Gutiérrez M, Suárez F, Arnal F, Fernández-García A, Aguirrezabalaga J, García-Buitrón J, Alvarez J, Máñez R. Liver transplantation from maastricht category 2 non-heart-beating donors: a source to increase the donor pool? *Transplant Proc* 2004; **36**: 747-750

9 **Kubal CA**, Harris RM, Inston NG, Graetz KP, Ready AR, Mellor SJ, Hamsho AS, Waring RH, World MJ. Mitochondrial complex activity in donor renal grafts, cold ischemia time, and recovery of graft function. *Transplantation* 2009; **87**: 1037-1039

10 **Reich DJ**, Munoz SJ, Rothstein KD, Nathan HM, Edwards JM, Hasz RD, Manzarbeitia CY. Controlled non-heart-beating donor liver transplantation: a successful single center experience, with topic update. *Transplantation* 2000; **70**: 1159-1166

11 **Hume DM**, Merrill JP, Miller BF, Thorn GW. Experiences with renal homotransplantation in the human: report of nine cases. *J Clin Invest* 1955; **34**: 327-382

12 **Daemen JH**, de Wit RJ, Bronkhorst MW, Marcar ML, Yin M, Heineman E, Kootstra G. Short-term outcome of kidney transplants from non-heart-beating donors after preservation by machine perfusion. *Transpl Int* 1996; **9** Suppl 1: S76-S80

13 **Pacholczyk MJ**, Lagiewska B, Szostek M, Chmura A, Morzycka-Michalik M, Rowińska-Stryjecka D, Wałaszewski J, Rowiński W. Transplantation of kidneys harvested from non-heart-beating donors: early and long-term results. *Transpl Int* 1996; **9** Suppl 1: S81-S83

14 **Gerstenkorn C**. Non-heart-beating donors: renewed source of organs for renal transplantation during the twenty-first century. *World J Surg* 2003; **27**: 489-493

15 **García-Valdecasas Salgado JC**. Non beating heart donors as a possible source for liver transplantation. *Acta Chir Belg* 2000; **100**: 268-271

16 **Merion RM**, Pelletier SJ, Goodrich N, Englesbe MJ, Delmonico FL. Donation after cardiac death as a strategy to increase deceased donor liver availability. *Ann Surg* 2006; **244**: 555-562

17 **D'Alessandro AM**, Hoffmann RM, Knechtle SJ, Eckhoff DE, Love RB, Kalayoglu M, Sollinger HW, Belzer FO. Successful extrarenal transplantation from non-heart-beating donors. *Transplantation* 1995; **59**: 977-982

18 **D'Alessandro AM**, Hoffmann RM, Knechtle SJ, Eckhoff DE, Love RB, Kalayoglu M, Sollinger HW, Belzer FO. Controlled non-heart-beating donors: a potential source of extrarenal organs. *Transplant Proc* 1995; **27**: 707-709

19 **Kootstra G**, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; **27**: 2893-2894

20 **Kootstra G**. Statement on non-heart-beating donor programs. *Transplant Proc* 1995; **27**: 2965

21 **Suárez F**, Otero A, Solla M, Arnal F, Lorenzo MJ, Marini M, Vázquez-Iglesias JL, Gómez M. Biliary complications after liver transplantation from maastricht category-2 non-heart-beating donors. *Transplantation* 2008; **85**: 9-14

22 **Gok MA**, Asher JF, Shenton BK, Rix D, Soomro NA, Jaques BC, Manas DM, Talbot D. Graft function after kidney transplantation from non-heartbeating donors according to maastricht category. *J Urol* 2004; **172**: 2331-2334

23 **Lanir A**, Jenkins RL, Caldwell C, Lee RG, Khettry U, Clouse ME. Hepatic transplantation survival: correlation with adenine nucleotide level in donor liver. *Hepatology* 1988; **8**: 471-475

24 **Hickman R**, Rose-Innes C, Tyler M, Bracher M, Lotz Z, Fourie J. Energy charge as an indication of liver viability. A comparison of changes in livers that remained intact with those subjected to autografting. *Transplantation* 1992; **53**: 540-545

25 **Ma Y**, Wang GD, Wu LW, Hu RD. Dynamical changing patterns of histological structure and ultrastructure of liver graft undergoing warm ischemia injury from non-heart-beating donor in rats. *World J Gastroenterol* 2006; **12**: 4902-4905

26 **Monbaliu D**, Libbrecht L, De Vos R, Vekemans K, Walter H, Liu Q, Heedfeld V, Goossens V, Pirenne J, Roskams T. The extent of vacuolation in non-heart-beating porcine donor liver grafts prior to transplantation predicts their viability. *Liver Transpl* 2008; **14**: 1256-1265

27 **Yska MJ**, Buis CI, Monbaliu D, Schuurs TA, Gouw AS, Kahmann ON, Visser DS, Pirenne J, Porte RJ. The role of bile salt toxicity in the pathogenesis of bile duct injury after non-heart-beating porcine liver transplantation. *Transplantation* 2008; **85**: 1625-1631

28 **McCord JM**. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985; **312**: 159-163

29 **Net M**, Valero R, Almenara R, Rull R, Gonzalez FJ, Taurá P, Lopez-Boado MA, Deulofeu R, Elena M, Capdevila L, Cabrer C, Visa J, García-Valdecasas JC. Hepatic xanthine levels as viability predictor of livers procured from non-heart-beating donor pigs. *Transplantation* 2001; **71**: 1232-1237

30 **Soejima Y**, Yanaga K, Wakiyama S, Nishizaki T, Yoshizumi T, Sugimachi K. Serum hyaluronic acid as a reliable parameter of allograft viability in porcine liver transplantation. *Hepatogastroenterology* 1996; **43**: 590-595

31 **Nagayama M**, Katsuramaki T, Kimura H, Isobe M, Meguro M, Matsuno T, Nui A, Hirata K. Prediction of graft viability from non-heart-beating donor pigs using hepatic microdialysate hypoxanthine levels. *J Surg Res* 2002; **107**: 210-218

32 **Golling M**, Kellner H, Fonouni H, Rad MT, Urbaschek R, Breitkreutz R, Gebhard MM, Mehrabi A. Reduced glutathione in the liver as a potential viability marker in non-heart-beating donors. *Liver Transpl* 2008; **14**: 1637-1647

33 **Zapletal C**, Heyne S, Breitkreutz R, Gebhard MM, Golling M. The influence of selenium substitution on microcirculation and glutathione metabolism after warm liver ischemia/reperfusion in a rat model. *Microvasc Res* 2008; **76**: 104-109

34 **Nishino T**, Nakanishi S, Okamoto K, Mizushima J, Hori H, Iwasaki T, Nishino T, Ichimori K, Nakazawa H. Conversion of xanthine dehydrogenase into oxidase and its role in reperfusion injury. *Biochem Soc Trans* 1997; **25**: 783-786

35 **de Vera ME**, Lopez-Solis R, Dvorchik I, Campos S, Morris W, Demetris AJ, Fontes P, Marsh JW. Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant* 2009; **9**: 773-781

36 **Qing DK**. Prolonging warm ischemia reduces the cold preservation limits of liver grafts in swine. *Hepatobiliary Pancreat Dis Int* 2006; **5**: 515-520

37 **Reddy S**, Greenwood J, Maniakin N, Bhattacharjya S, Zilvetti M, Brockmann J, James T, Pigott D, Friend P. Non-heart-beating donor porcine livers: the adverse effect of cooling. *Liver Transpl* 2005; **11**: 35-38

38 **Barlow AD**, Metcalfe MS, Johari Y, Elwell R, Veitch PS, Nicholson ML. Case-matched comparison of long-term results of non-heart beating and heart-beating donor renal transplants. *Br J Surg* 2009; **96**: 685-691

39 **Bhogal RH**, Sutaria R, Gunson BK, Bramhall SR. Similar liver transplantation survival with selected cardiac death donors and brain death donors (Br J Surg 2010; 97: 744-753). *Br J Surg* 2010; **97**: 1310; author reply 1310-1311

40 **Abt P**, Crawford M, Desai N, Markmann J, Olthoff K, Shaked A. Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. *Transplantation* 2003; **75**: 1659-1663

41 **Maheshwari A**, Maley W, Li Z, Thuluvath PJ. Biliary complications and outcomes of liver transplantation from donors after cardiac death. *Liver Transpl* 2007; **13**: 1645-1653

42 **Lee HW**, Suh KS, Shin WY, Cho EH, Yi NJ, Lee JM, Han JK, Lee KU. Classification and prognosis of intrahepatic biliary stricture after liver transplantation. *Liver Transpl* 2007; **13**: 1736-1742

43 **Muiesan P**, Girlanda R, Baker A, Rela M, Heaton N. Successful segmental auxiliary liver transplantation from a non-heart-beating donor: implications for split-liver transplantation. *Transplantation* 2003; **75**: 1443-1445

44 **Muiesan P**, Jassem W, Girlanda R, Steinberg R, Vilca-Melendez H, Mieli-Vergani G, Dhawan A, Rela M, Heaton N. Segmental liver transplantation from non-heart beating donors--an early experience with implications for the future. *Am J Transplant* 2006; **6**: 1012-1016

45 **Gozzini S**, Perera MT, Mayer DA, Mirza DF, Kelly DA, Muiesan P, Sharif K. Liver transplantation in children using non-heart-beating donors (NHBD). *Pediatr Transplant* 2010; **14**: 554-557

46 **Perera MT**, Gozzini S, Mayer D, Sharif K, Bennett J, Muiesan P, Mirza DF. Safe use of segmental liver grafts from donors after cardiac death (DCD) in children with acute liver failure. *Transpl Int* 2009; **22**: 757-760

47 **Brook NR**, Waller JR, Nicholson ML. Nonheart-beating kidney donation: current practice and future developments. *Kidney Int* 2003; **63**: 1516-1529

48 **Balupuri S**, Buckley P, Mohamed M, Cornell C, Mantle D, Kirby J, Manas DM, Talbot D. Assessment of non-heart-beating donor (NHBD) kidneys for viability on machine perfusion. *Clin Chem Lab Med* 2000; **38**: 1103-1106

49 **Balupuri S**, Buckley P, Mohamad M, Chidambaram V, Gerstenkorn C, Sen B, Kirby J, Manas DM, Talbot D. Early results of a non-heartbeating donor (NHBD) programme with machine perfusion. *Transpl Int* 2000; **13** Suppl 1: S255-S258

50 **Ali A**, White P, Dhital K, Ryan M, Tsui S, Large S. Cardiac recovery in a human non-heart-beating donor after extracorporeal perfusion: source for human heart donation? *J Heart Lung Transplant* 2009; **28**: 290-293

51 **Imber CJ**, St Peter SD, Lopez de Cenarruzabeitia I, Pigott D, James T, Taylor R, McGuire J, Hughes D, Butler A, Rees M, Friend PJ. Advantages of normothermic perfusion over cold storage in liver preservation. *Transplantation* 2002; **73**: 701-709

52 **Imber CJ**, St Peter SD, de Cenarruzabeitia IL, Lemonde H, Rees M, Butler A, Clayton PT, Friend PJ. Optimisation of bile production during normothermic preservation of porcine livers. *Am J Transplant* 2002; **2**: 593-599

53 **Reddy SP**, Bhattacharjya S, Maniakin N, Greenwood J, Guerreiro D, Hughes D, Imber CJ, Pigott DW, Fuggle S, Taylor R, Friend PJ. Preservation of porcine non-heart-beating donor livers by sequential cold storage and warm perfusion. *Transplantation* 2004; **77**: 1328-1332

54 **Gong J**, Lao XJ, Wang XM, Long G, Jiang T, Chen S. Preservation of non-heart-beating donor livers in extracorporeal liver perfusion and histidine-trytophan-ketoglutarate solution. *World J Gastroenterol* 2008; **14**: 2338-2342

55 **St Peter SD**, Imber CJ, Lopez I, Hughes D, Friend PJ. Extended preservation of non-heart-beating donor livers with normothermic machine perfusion. *Br J Surg* 2002; **89**: 609-616

56 **Balupuri S**, Strong A, Hoernich N, Snowden C, Mohamed M, Manas D, Kirby J, Talbot D. Machine perfusion for kidneys: how to do it at minimal cost. *Transpl Int* 2001; **14**: 103-107

57 **Lindell SL**, Compagnon P, Mangino MJ, Southard JH. UW solution for hypothermic machine perfusion of warm ischemic kidneys. *Transplantation* 2005; **79**: 1358-1361

58 **Dutkowski P**, Furrer K, Tian Y, Graf R, Clavien PA. Novel short-term hypothermic oxygenated perfusion (HOPE) system prevents injury in rat liver graft from non-heart beating donor. *Ann Surg* 2006; **244**: 968-976; discussion 976-977

59 **Miyagi S**, Iwane T, Akamatsu Y, Nakamura A, Sato A, Satomi S. The significance of preserving the energy status and microcirculation in liver grafts from non-heart-beating donor. *Cell Transplant* 2008; **17**: 173-178

60 **Manekeller S**, Dobberahn V, Hirner A, Minor T. Liver integrity after warm ischemia in situ and brief preservation ex vivo: the value of aerobic post-conditioning. *Cryobiology* 2007; **55**: 249-254

61 **Jain S**, Xu H, Duncan H, Jones JW, Zhang JX, Clemens MG, Lee CY. Ex-vivo study of flow dynamics and endothelial cell structure during extended hypothermic machine perfusion preservation of livers. *Cryobiology* 2004; **48**: 322-332

62 **Ko WJ**, Chen YS, Tsai PR, Lee PH. Extracorporeal membrane oxygenation support of donor abdominal organs in non-heart-beating donors. *Clin Transplant* 2000; **14**: 152-156

63 **Ko WJ**, Chen YS, Chen RJ, Lai MK, Lee PH. Non-heart-beating donors under extracorporeal membrane oxygenation support. *Transplant Proc* 2002; **34**: 2600-2601

64 **Quintela J**, Gala B, Baamonde I, Fernández C, Aguirrezabalaga J, Otero A, Suárez F, Fernández A, Gomez M. Long-term results for liver transplantation from non-heart-beating donors maintained with chest and abdominal compression-decompression. *Transplant Proc* 2005; **37**: 3857-3858

65 **Rojas A**, Chen L, Bartlett RH, Arenas JD. Assessment of liver function during extracorporeal membrane oxygenation in the non-heart beating donor swine. *Transplant Proc* 2004; **36**: 1268-1270

66 **Rojas-Pena A**, Reoma JL, Krause E, Boothman EL, Padiyar NP, Cook KE, Bartlett RH, Punch JD. Extracorporeal support: improves donor renal graft function after cardiac death. *Am J Transplant* 2010; **10**: 1365-1374

67 **Gok MA**, Shenton BK, Peaston R, Cornell C, Robertson H, Mathers M, Aitchison JD, Dark JH, Mantle D, Talbot D. Improving the quality of kidneys from non-heart-beating donors, using streptokinase: an animal model. *Transplantation* 2002; **73**: 1869-1874

68 **Yamauchi J**, Schramm R, Richter S, Vollmar B, Menger MD, Minor T. Improvement of microvascular graft equilibration and preservation in non-heart-beating donors by warm preflush with streptokinase. *Transplantation* 2003; **75**: 449-453

69 **Gok MA**, Shenton BK, Buckley PE, Peaston R, Cornell C, Soomro N, Jaques BC, Manas DM, Talbot D. How to improve the quality of kidneys from non-heart-beating donors: a randomised controlled trial of thrombolysis in non-heart-beating donors. *Transplantation* 2003; **76**: 1714-1719

70 **Minor T**, Hachenberg A, Tolba R, Pauleit D, Akbar S. Fibrinolytic preflush upon liver retrieval from non-heart beating donors to enhance postpreservation viability and energetic recovery upon reperfusion. *Transplantation* 2001; **71**: 1792-1796

71 **Yamauchi JI**, Richter S, Vollmar B, Menger MD, Minor T. Warm preflush with streptokinase improves microvascular procurement and tissue integrity in liver graft retrieval from non-heart-beating donors. *Transplantation* 2000; **69**: 1780-1784

72 **Pirenne J**, Monbaliu D, Aerts R, Desschans B, Liu Q, Cassiman D, Laleman W, Verslype C, Magdy M, Van Steenbergen W, Nevens F. Biliary strictures after liver transplantation: risk factors and prevention by donor treatment with epoprostenol. *Transplant Proc* 2009; **41**: 3399-3402

73 **Gong J**, Lao XJ, Zhang SJ, Chen S. Protective effects of L-arginine against ischemia-reperfusion injury in non-heart beating rat liver graft. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 481-484

74 **Asher J**, Oliver A, Wilson C, Gupta A, Gok M, Balupuri S, Shenton B, Del Rio Martin J, Rix D, Soomro N, Jaques B, Manas D, Ward M, Talbot D. A simple cardiovascular risk score can predict poor outcome in NHBD renal transplantation. *Transplant Proc* 2005; **37**: 3292-3293

75 **Gheorghita E**, Rata O, Trifu M. [Intensive care issues in the

management of potential organ donors]. *Chirurgia* (Bucur) 2010; **105**: 225-228
76 **Dictus C**, Vienenkoetter B, Esmaeilzadeh M, Unterberg A, Ahmadi R. Critical care management of potential organ donors: our current standard. *Clin Transplant* 2009; **23** Suppl 21: 2-9
77 **Varelas PN**, Abdelhak T, Hacein-Bey L. Withdrawal of life-sustaining therapies and brain death in the intensive care unit. *Semin Neurol* 2008; **28**: 726-735
78 **Mascia L**, Mastromauro I, Viberti S, Vincenzi M, Zanello M. Management to optimize organ procurement in brain dead donors. *Minerva Anestesiol* 2009; **75**: 125-133
79 **Rady MY**, Verheijde JL, McGregor J. Organ procurement after cardiocirculatory death: a critical analysis. *J Intensive Care Med* 2008; **23**: 303-312
80 **Collins TJ**. Organ and tissue donation: a survey of nurse's knowledge and educational needs in an adult ITU. *Intensive Crit Care Nurs* 2005; **21**: 226-233

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v3.i11.177

World J Gastrointest Surg 2011 November 27; 3(11): 177-182
ISSN 1948-9366 (online)

BRIEF ARTICLE

Laparoscopic total colectomy: Does the indication influence the outcome?

Eddy Cotte, Faheez Mohamed, Stéphane Nancey, Yves François, Olivier Glehen, Bernard Flourié, Jean-Christophe Saurin, Gilles Poncet

Eddy Cotte, Yves François, Olivier Glehen, Department of Digestive Surgery, Centre Hospitalo-Universitaire Lyon Sud, Hospices Civils de Lyon, 69495 Pierre Bénite Cedex, France
Eddy Cotte, Yves François, Olivier Glehen, EA 3738, Université Claude Bernard Lyon1, Faculté de Médecine Lyon Sud, BP 12, 69921 Oullins Cedex, France
Faheez Mohamed, Colorectal Research Unit, Basingstoke and North Hampshire Foundation Trust, Aldermaston Road, Basingstoke RG24 9NA, Hampshire, United Kingdom
Stéphane Nancey, Bernard Flourié, Department of Gastroenterology, Centre Hospitalo-Universitaire Lyon-Sud, Hospices Civils de Lyon, 69495 Pierre Bénite Cedex, France
Jean-Christophe Saurin, Gilles Poncet, Digestive Federation, Centre Hospitalo-Universitaire Edouard Herriot, Hospices Civils de Lyon, 69008 Lyon, France
Author contributions: Cotte E and Poncet G analyzed the data and drafted the article; Mohamed F participated in the revision of article and checked the paper for linguistic accuracy; François Y, Glehen O and Saurin JC participated in the acquisition of the data and revision of the article; Nancey S and Flourié B participated in the interpretation of the data and revision of the article; all authors read and approved the final manuscript.
Correspondence to: Eddy Cotte, MD, PhD, Department of Digestive Surgery, Centre Hospitalo-Universitaire Lyon Sud, Hospices Civils de Lyon, 69495 Pierre Bénite Cedex, France. eddy.cotte@chu-lyon.fr
Telephone: +33-478-861385 Fax: +33-478-863343
Received: July 22, 2011 Revised: October 24, 2011
Accepted: October 29, 2011
Published online: November 27, 2011

Abstract

AIM: To assess and compare outcomes of laparoscopic total colectomy performed for a variety of indications.

METHODS: Sixty six patients underwent laparoscopic total colectomy for inflammatory bowel disease (IBD) (13) and other diseases (53). Data on demographics, pre- and post-operative outcomes were collected prospectively.

RESULTS: Mean operative time was 4.5 h. Conversion rate was 13.6%. Total colectomy performed for IBD was associated with a significantly higher anastomotic leak rate (23.1% *vs* 1.9%, $P < 0.05$). On univariate analysis, hand sewn anastomosis and treatment with more than 20 mg of prednisolone for at least 3 mo was associated with a higher anastomotic leak rate ($P < 0.05$). No significant difference was found in return of gut function and overall morbidity between disease groups.

CONCLUSION: Laparoscopic total colectomy is feasible and outcomes are equivalent whatever the indication, except for anastomotic leak rate which is higher for patients with IBD.

Key words: Colectomy; Inflammatory bowel disease; Laparoscopy; Familial adenomatous polyposis; Constipation; Colonic neoplasms; Hereditary nonpolyposis; Diverticulosis; Treatment outcomes

Peer reviewer: Tsukasa Hotta, MD, PhD, Department of Surgery, Wakayama Medical University, School of Medicine, 811-1, Kimiidera, Wakayama 641-8510, Japan

Cotte E, Mohamed F, Nancey S, François Y, Glehen O, Flourié B, Saurin JC, Poncet G. Laparoscopic total colectomy: Does the indication influence the outcome? *World J Gastrointest Surg* 2011; 3(11): 177-182 Available from: URL: http://www.wjgnet.com/1948-9366/full/v3/i11/177.htm DOI: http://dx.doi.org/10.4240/wjgs.v3.i11.177

INTRODUCTION

Numerous studies have demonstrated the benefits of laparoscopic segmental colonic resection for benign and malignant disease[1,2]. Proven advantages include im-

proved cosmesis, decreased blood loss and a reduction in postoperative pain, fatigue and time to resumption of oral intake. In contrast, data concerning laparoscopic total colectomy has been less compelling. Common indications for total colectomy include familial adenomatous polyposis (FAP), Lynch syndrome, slow transit constipation and inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis (UC). Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the treatment of choice in UC. For selected patients presenting with mild disease in the rectum, no dysplasia and with normal rectal compliance, a subtotal colectomy with ileo-distal sigmoid anastomosis may be an alternative and was performed in this study. Few published reports exist and mainly report techniques performed for a single indication or include small numbers of patients[3-10]. The aim of this study was to report the outcomes of laparoscopic total colectomy based on indication, comparing IBD with other indications.

MATERIALS AND METHODS

Patients

Between June 1998 and June 2007, 66 consecutive patients underwent a laparoscopic total or subtotal colectomy for benign or malignant disease. Patients were admitted to two surgical departments of Hospices Civils de Lyon and operated on by several surgeons (Digestive Surgical Department of Centre Hospitalier Lyon-Sud and Digestive Surgical Department of Centre Hospitalier Edouard Herriot). Thirteen patients (19.7%) presented with IBD (11 with UC and 2 with colonic Crohn's disease), 40 patients (60.6%) with FAP, 7 patients (10.6%) with slow transit constipation, 5 patients (7.6%) with colonic cancer and Lynch syndrome and 1 patient (1.5%) with diffuse colonic diverticulosis. Patients with IBD were operated on for failure of medical treatment. All patients with IBD except 1 patient with UC received at least 3 mo of maintenance steroid treatment [prednisolone, mean 24.2 mg daily (SD = 11.1)]. The dosage of prednisolone used was > 20 mg for 7 patients and ≤ 20 mg for 5 patients. Six patients (46%) with IBD had an immunosuppressive treatment [azathioprine (n = 5) and cyclosporine (n = 1)]. No patient with UC had fulminant disease as defined by two or more of the following findings: tachycardia (heart rate > 120 beats per minute), temperature greater than 38.0℃, peritoneal signs and white blood cell count greater than 11 000/mL.

Surgical technique

All patients underwent bowel preparation with polyethylene glycol or sodium phosphate. Under general anesthesia, patients were placed in a modified lithotomy position with legs slightly abducted and arms tucked to the sides. A nasogastric tube was inserted during surgery but postoperative use depended on the individual surgeon's routine practice. Pneumoperitoneum was established with a Veress needle at an abdominal pressure of 12 mmHg. A 10 mm port was placed at the umbilicus for the 30° oblique viewing laparoscope. Four additional ports were placed under laparoscopic vision: one 12 m port in the right lower quadrant, one 10 mm port in the right and left upper quadrants and one 5 mm port in the suprapubic position. Dissection and division of the mesentery was performed with a 10 mm laparoscopic Ligasure device (Ligasure Atlas; Valleylab, Boulder, CO, United States) or a 5 mm blade Harmonic Scalpel (Ultracision Shears Harmonic Scalpel LCS; Ethicon Endosurgery SA, Issy-Les-Moulineaux, France) according to the surgeon's preference, without mesenteric lymphadenectomy except for malignancy. Total colectomy was performed from right to left (lateral to medial dissection). The procedure involved right colonic mobilization as well as hepatic flexure mobilization followed by transverse colonic dissection. The omentum was elevated off the transverse colon (except for cancers involving the transverse colon). The splenic flexure and finally the left colonic dissection were followed by division at the rectosigmoid junction using a laparoscopic linear stapler. Patients had either an ileo-distal sigmoid or ileorectal anastomosis. For an ileo-distal sigmoid anastomosis (subtotal colectomy), a short lower midline incision was made for exteriorisation and resection of the specimen and formation of a hand sewn anastomosis. For an ileorectal anastomosis (total colectomy), the bowel was divided at the rectosigmoid junction and the specimen removed through a short transverse incision in the right lower quadrant. After re-establishment of the pneumoperitoneum, a stapled end-to-end ileorectal anastomosis was performed with an endoluminal stapling gun. A pelvic drain was used selectively.

Outcome measures

Demographics, including age, gender and indication for colectomy, were collected prospectively for all patients.

The principle outcome measures were: (1) Intraoperative data: operative time, surgical procedure performed, conversions and their reasons, creation of a stoma; and (2) Early postoperative: time to first bowel movement and time with nasogastric tube, complications, anastomotic leak, radiological intervention, reoperation, length of hospital stay.

The period of inclusion was divided into two 5-year periods: 1998 to 2002 and 2003 to 2007.

Statistical analysis

Statistical analysis was performed using SPSS version17.0 (SPSS Inc., Chicago, IL, United States). Results are expressed as the mean ± SD. Comparisons between groups were performed using the Student t test for continuous data and χ^2 or Fisher exact test for categorical data. Multivariate analysis was performed using a logistic regression. A P value < 0.05 was considered statistically significant.

RESULTS

Intraoperative data

Mean operative time was 4.5 h (Table 1). Length of op-

Table 1 Demographic and intraoperative data (mean ± SD) *n* (%)

	Crohn (*n* = 2)	Ulcerative colitis (*n* = 11)	FAP (*n* = 40)	Lynch syndrome (*n* = 5)	Constipation (*n* = 7)	Diverticulosis (*n* = 1)	All (*n* = 66)
Age (yr)	28.0 ± 9.7	42.5 ± 12.7	46.1 ± 19.4	44.8 ± 19.6	36.4 ± 8.9	57.0 ± 0.0	44.4 ± 17.0
Female	0	3 (27.3)	17 (42.5)	1 (20)	7 (100)	0	28 (42.4)
Operative time (h)	4.0 ± 0.0	4.6 ± 0.5	4.5 ± 1.5	4.1 ± 1.3	4.2 ± 1.0	5.0 ± 0.0	4.5 ± 1.24
Stoma	1 (50.0)	0	0	0	0	0	1 (1.5)
Conversion	0	2 (18.2)	6 (15)	0	1 (14.3)	0	9 (13.6)
Anastomosis							
Ileorectal	0	3 (27.3)	37 (92.5)	4 (80)	1 (14.3)	1 (100)	46 (69.7)
Ileo-distal sigmoid	2 (100)	8 (72.7)	3 (7.5)	1 (20)	6 (85.7)	0	20 (30.3)

FAP: Familial ademotous polyposis.

Table 2 Outcomes based on indication for surgery (mean ± SD) *n* (%)

	Inflammatory bowel disease (*n* = 13)	Other indications (*n* = 53)	*P* value
Age (yr)	42.5 (12.6)	44.9 (18.3)	0.663
Female	3 (23.1)	25 (47.2)	0.115
Operative time (h)	4.5 ± 0.5	4.40 ± 1.36	0.899
Conversion	2 (15.4)	7 (13.2)	> 0.999
Length of stay (d)	15.2 ± 7.5	12.8 ± 6.7	0.274
Time to first bowel movement (days from surgery)	4.9 ± 3.1	4.3 ± 3.1	0.522
Nasogastric tube[1]	9 (69.2)	25 (47.2)	0.154
Overall morbidity	5 (38.5)	19 (35.8)	> 0.999
Anastomotic leak	3 (23.1)	1 (1.9)	0.022
Reoperation	3 (23.1)	6 (11.3)	0.364
Radiological drainage	1 (7.7)	3 (5.7)	> 0.999

[1]Numbers of patients (%) requiring a nasogastric tube for more than 1 postoperative day when inserted intraoperatively or requiring postoperative insertion.

Table 3 Comparison of outcomes over 2 consecutive time periods (mean ± SD) *n* (%)

	1998-2002 (*n* = 21)	2003-2007 (*n* = 45)	*P* value
Inflammatory bowel disease	10 (47.6)	3 (6.7)	< 0.0001
Operative time (h)	5.0 ± 0.9	4.2 ± 1.3	0.0156
Conversion	4 (19.0)	5 (11.1)	0.4499
Length of stay (d)	16.5 ± 7.9	11.8 ± 5.9	0.0093
Time to first bowel movement (days from surgery)	5.1 ± 3.5	4.1 ± 2.8	0.2439
Overall morbidity	10 (47.6)	14 (31.1)	0.1941
Anastomotic leak	2 (9.5)	2 (4.4)	0.5865
Reoperation	5 (23.8)	4 (8.9)	0.1300

eration was not statistically different for IBD compared to other indications (Table 2). One protecting loop ileostomy was performed for Crohn's disease. Conversion rate was 13.6% (9 patients). Seven conversions were due to intra-abdominal adhesions. Super obesity (body mass index > 50) was responsible for one conversion and rectal trauma during stapling of an ileorectal anastomosis for the other. The conversion rate was not statistically different between IBD and other indications. Ileo-distal sigmoid anastomosis was the most common used for IBD [10/13 patients (76.9%)] and slow transit constipation [6/7 patients (85.7%)]. For other indications, an ileorectal anastomosis was most often performed [42/46 patients (91.3%)]. These results were compared between the 2 periods of inclusion (Table 3). Length of operation was shorter after 2002 (4.2 h *vs* 5.0 h, $P = 0.0156$). There was no significant difference in conversion rate between the two time periods.

Early postoperative outcomes

Early postoperative results are reported in Table 4. There were no postoperative deaths (30 d mortality). A nasogastric (N-G) tube was left *in situ* postoperatively in 43 patients (65.1%). In 17 patients it was removed on the first postoperative day. Twenty-six patients had postoperative small bowel ileus resulting in the N-G tube being left for a median of 3 d after surgery. Of the 23 patients whose N-G tube was removed immediately after surgery, 8 (34.8%) required re-insertion. Therefore, an N-G tube was considered useful in 34 patients (51.5%).

Although the overall complication rate (36.4%) was not statistically greater for patients with IBD (Table 2), anastomotic leak was more frequent following surgery for UC and Crohn's disease (23.1% *vs* 1.9%, $P = 0.022$). On univariate analysis, anastomotic leaks were also significantly correlated with the type of anastomosis (4/20 anastomotic leaks for hand sewn anastomosis *vs* 0/46 for stapled anastomosis, $P = 0.0067$) and maintenance treatment with steroids > 20 mg (3/7 *vs* 1/59, $P = 0.0029$). On multivariate analysis, none of these parameters appeared to significantly increase the anastomotic leak rate. Complications that increased the length of stay were reported (Table 4). In patients with UC, these were profuse diarrhea lasting 10 d (1) and prolonged ileus (1). In patients with FAP: aspiration pneumonia (1), prolonged ileus (1), segmental portal vein thrombosis (1) and intra-abdominal abscess without anastomotic leak (4) requiring reoperation in 2 patients, percutaneus radiological drainage in 1 and treatment with antibiotics in another. In patients with Lynch syndrome: intra-abdominal abscess without anastomotic leak treated by antibiotics only (1), lymph leak which delayed intra-abdominal drain removal (1) and small bowel obstruction treated non-operatively (1). For diverticulosis: intra-abdominal bleeding requiring

Table 4 Early postoperative results (mean ± SD) *n* (%)

	Crohn (*n* = 2)	Ulcerative colitis (*n* = 11)	FAP (*n* = 40)	Lynch syndrome (*n* = 5)	Constipation (*n* = 7)	Diverticulosis (*n* = 1)	All (*n* = 66)
Length of stay (d)	17.5 ± 9.2	14.7 ± 7.6	11.2 ± 4.4	12.8 ± 6.9	13.7 ± 7.9	13 ± 0	13.3 ± 6.7
First bowel movement (d)	5.5 ± 3.5	4.8 ± 3.2	3.7 ± 2.7	4.6 ± 3.2	7.1 ± 4.1	5 ± 0	4.4 ± 3.1
Nasogastric tube[1]	1 (50)	7 (63.6)	19 (47.5)	1 (20)	4 (57.1)	1 (100)	34 (51.5)
Complications	2 (100)	3 (27.3)	11 (27.5)	4 (80)	3 (43)	1 (100)	24 (36.4)
Anastomotic leak	2 (100)	1 (9.1)	0	0	1 (14.3)	0	4 (6.1)
Wound abscess	0	0	2 (5)	1 (20)	1 (14.3)	0	4 (6.1)
Surgery for bowel obstruction	0	0	1 (2.5)	0	1 (14.3)	0	2 (3)
Other complications	0	2 (18.2)	8 (20)	3 (60)	0	1 (100)	14 (21.2)
Reoperation	2 (100)	1 (9.1)	3 (7.5)	0	2 (28.6)	1 (100)	9 (13.6)
Radiological intervention	1 (50)	0	3 (7.5)	0	0	0	4 (6.1)

[1]Numbers of patients (%) requiring a nasogastric tube for more than 1 postoperative day when inserted intraoperatively or requring postoperative insertion. FAP: Familial adenomatous polyposis.

Table 5 Studies of total and segmental colectomy

Authors	Indication	No. of patients	Procedure	Conversion (%)	Morbidity (%)	Anastomotic leaks (%)	Reoperation (%)	Hospital stay (d)
Hamel *et al*[3]	Crohn	21	STC (L)	24	33	10	10	8.8
Pokala *et al*[11]	FAP, C, Lynch, IBD	34	TC + STC (L)	11.8	26.5	5.9	8.8	4.1
		34	TC + STC (O)	NA	38.2	0	11.8	6.8
Hsiao *et al*[4]	C	44	TC (HA)	0	18.2	2.3	6.8	7.6
Delaney *et al*[1]	Cancer, IBD, DD	11 044	SegC (L)	10.1	26	0.26	0.5	6.3
		21 689	SegC (O)	NA	31.8	0.18	0.3	8.5
Current series	IDB	13	TC + STC (L)	15.2	38.5	23.1	23.1	15.2
	Non IBD	53		13.2	35.8	1.9	11.3	12.8
	All	66		13.6	36.4	6.1	13.6	13.3

STC: Subtotal colectomy; TC: Total colectomy; SegC: Segmental colectomy; L: Laparoscopic; O: Open; HA: Hand assisted; FAP: Familial adenomatous polyposis; C: Slow transit Constipation; IBD: Inflammatory bowel disease; DD: Diverticular disease; NA: Not applicable.

re-operation (1). Nine reoperations were necessary: 4 for peritonitis after an anastomotic leak, 2 intra-abdominal abscesses without anastomotic leak, 2 for small bowel obstruction and 1 for intra-abdominal bleeding.

Length of hospital stay was 13.3 d (SD = 6.7) with no significant difference between patients with and without IBD (Table 2). Length of hospital stay was shorter after 2002 (11.8 d *vs* 16.5 d, $P = 0.0093$) (Table 3). No significant difference was found between these 2 periods in the time to first bowel movement, overall morbidity, anastomotic leak rate and reoperation rate.

DISCUSSION

This study reports the results of 66 consecutive patients who underwent a laparoscopic total colectomy. Our data shows that this operation is feasible and safe with no mortality and acceptable morbidity, as reported in previous studies[3-11] (Table 5). The early postoperative results highlight problems with bowel function after total colectomy with a mean of 4.4 d until the first bowel movement. 51.5 % of patients needed a nasogastric tube. Recovery of gut function seems longer than following segmental laparoscopic colectomy when patients rarely require nasogastric tube insertion (less than 15%) and can be discharged on the fourth postoperative day[12,13]. No enhanced recovery protocol was followed in this study. These protocols have demonstrated their benefit in improving outcomes after segmental colonic resection[14,15]. They reduce the time to restoration of bowel function and the length of hospital stay. No studies have evaluated these protocols for total colectomy with the majority of controlled trials including only segmental colectomies. It is therefore difficult to extrapolate the results of these trials to the management of patients after total colectomy. However, length of stay and restoration of bowel function appear longer in our series than in previous published series of total colectomies (Table 5). This may be explained by the long time period over which our study was conducted. When analyzed in two consecutive 5-year time periods (Table 3), a decrease in operative time and length of hospital stay was observed. This is likely due to an improvement in operative technique (riding the learning curve) and in postoperative care. Although no formal enhanced recovery protocol was followed, there was a definite evolution in postoperative care in our unit based on elements of enhanced recovery such as early enteral feeding and mobilization with avoidance of opiate analgesia. Enhanced recovery protocols have demonstrated their utility following segmental colectomy and may also improve outcomes following laparoscopic total colectomy. A randomised controlled trial is necessary to evaluate

this. Refinement in patient selection in our unit may also explain fewer patients with IBD undergoing surgery over time.

IBD is not a common indication for total colectomy. In our series, it was performed principally for UC. Restorative proctocolectomy with IPAA is the treatment of choice in UC. However, in patients, especially young women, with mild rectal disease, no dysplasia and normal rectal compliance, a subtotal colectomy may be an alternative to IPAA that may give better functional results with reduced risk of infertility. Evaluation of the long-term results of total colectomy for UC was not the aim of this study and would require a controlled trial with large numbers of patients.

Morbidity in this study was higher than for segmental colectomy with a reoperation rate of 13.6% (0.5% in a recent study using a large national database of 11 044 segmental laparoscopic colectomies[1]), but equivalent to other studies of total colectomy for IBD (Table 5).

We compared IBD with other indications for total colectomy. No difference in operative time, conversion rate, the length of stay or overall morbidity was seen. However, there were significantly more anastomotic leaks in patients with IBD, especially Crohn's disease. Both patients with Crohn's disease suffered anastomotic leaks although one had a defunctioning stoma. Several studies report high morbidity rates (up to 35%), with a conversion rate reaching 30% for laparoscopic surgery in Crohn's disease[3,8,16-18]. In our opinion, all patients with Crohn's disease who undergo total colectomy should be prepared for a defunctioning stoma. For patients without IBD, the anastomotic leak rate (1.9%) was equivalent to segmental colectomy which varies between 0% and 7%[1,19]. A hand sewn anastomosis and maintenance treatment with more than 20 mg of prednisolone daily were risk factors for anastomotic leak in univariate but not multivariate analysis. Patients with IBD were more likely to possess both these factors but larger numbers are required to evaluate these factors fully. Tilney *et al*[10], in a meta-analysis of outcomes after laparoscopic or open total colectomy, reported 63 patients who underwent a restorative laparoscopic total colectomy. Our series is one of the largest reporting laparoscopic total colectomy in the literature and involved two surgical centers although a large multicenter prospective study would help clarify many issues raised.

In conclusion, laparoscopic total colectomy is feasible even for patients with IBD but complication rates are higher and return to normal gut function slower than for segmental colectomy. Outcomes are equivalent whatever the indication, except for anastomotic leak rate which is higher for patients with IBD. To achieve the best outcomes in this group, careful patient selection with a low threshold for a defunctioning stoma is essential.

COMMENTS

Background

Numerous studies have demonstrated the benefits of laparoscopic segmental colonic resection for benign and malignant disease. Proven advantages include improved cosmesis, decreased blood loss and a reduction in postoperative pain, fatigue and time to resumption of oral intake. In contrast, data concerning laparoscopic total colectomy has been less compelling. The aim of this study was to report the outcomes of laparoscopic total colectomy based on indication, comparing inflammatory bowel disease (IBD) with other indications.

Research frontiers

In the area of mini-invasive surgery, laparoscopy was applied to colorectal surgery. The aim was to reduce the surgical stress to improve the post-operative course.

Innovations and breakthroughs

Based on a large series, this study describes the outcomes of laparoscopic total colectomy and is a reference for comparison in future studies.

Applications

The study results show that laparoscopic total colectomy is feasible and outcomes are equivalent whatever the indication, except for anastomotic leak rate which is higher for patients with IBD. The study results suggest that all patients with Crohn's disease who undergo total colectomy should be prepared for a defunctioning stoma.

Peer review

This paper demonstrates the outcomes of laparoscopic total colectomy performed for a variety of indications.

REFERENCES

1 **Delaney CP**, Chang E, Senagore AJ, Broder M. Clinical outcomes and resource utilization associated with laparoscopic and open colectomy using a large national database. *Ann Surg* 2008; **247**: 819-824

2 **Noel JK**, Fahrbach K, Estok R, Cella C, Frame D, Linz H, Cima RR, Dozois EJ, Senagore AJ. Minimally invasive colorectal resection outcomes: short-term comparison with open procedures. *J Am Coll Surg* 2007; **204**: 291-307

3 **Hamel CT**, Hildebrandt U, Weiss EG, Feifelz G, Wexner SD. Laparoscopic surgery for inflammatory bowel disease. *Surg Endosc* 2001; **15**: 642-645

4 **Hsiao KC**, Jao SW, Wu CC, Lee TY, Lai HJ, Kang JC. Hand-assisted laparoscopic total colectomy for slow transit constipation. *Int J Colorectal Dis* 2008; **23**: 419-424

5 **McNevin MS**, Bax T, MacFarlane M, Moore M, Nye S, Clyde C, Lin P, Beyersdorf S, Ahmad R, Bates D. Outcomes of a laparoscopic approach for total abdominal colectomy and proctocolectomy. *Am J Surg* 2006; **191**: 673-676

6 **Ng SS**, Li JC, Lee JF, Yiu RY, Leung KL. Laparoscopic total colectomy for colorectal cancers: a comparative study. *Surg Endosc* 2006; **20**: 1193-1196

7 **Pinedo G**, Zarate AJ, Garcia E, Molina ME, Lopez F, Zúñiga A. Laparoscopic total colectomy for colonic inertia: surgical and functional results. *Surg Endosc* 2009; **23**: 62-65

8 **Rosman AS**, Melis M, Fichera A. Metaanalysis of trials comparing laparoscopic and open surgery for Crohn's disease. *Surg Endosc* 2005; **19**: 1549-1555

9 **Seshadri PA**, Poulin EC, Schlachta CM, Cadeddu MO, Mamazza J. Does a laparoscopic approach to total abdominal colectomy and proctocolectomy offer advantages? *Surg Endosc* 2001; **15**: 837-842

10 **Tilney HS**, Lovegrove RE, Purkayastha S, Heriot AG, Darzi AW, Tekkis PP. Laparoscopic vs open subtotal colectomy for benign and malignant disease. *Colorectal Dis* 2006; **8**: 441-450

11 **Pokala N**, Delaney CP, Senagore AJ, Brady KM, Fazio VW. Laparoscopic vs open total colectomy: a case-matched comparative study. *Surg Endosc* 2005; **19**: 531-535

12 **Basse L**, Jakobsen DH, Bardram L, Billesbølle P, Lund C, Mogensen T, Rosenberg J, Kehlet H. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. *Ann Surg* 2005; **241**: 416-423

13 **Raue W**, Haase O, Junghans T, Scharfenberg M, Müller JM, Schwenk W. 'Fast-track' multimodal rehabilitation program improves outcome after laparoscopic sigmoidectomy: a controlled prospective evaluation. *Surg Endosc* 2004; **18**:

1463-1468
14 **Gouvas N**, Tan E, Windsor A, Xynos E, Tekkis PP. Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis* 2009; **24**: 1119-1131
15 **Wind J**, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, Gouma DJ, Bemelman WA. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* 2006; **93**: 800-809
16 **Eshuis EJ**, Polle SW, Slors JF, Hommes DW, Sprangers MA, Gouma DJ, Bemelman WA. Long-term surgical recurrence, morbidity, quality of life, and body image of laparoscopic-assisted vs. open ileocolic resection for Crohn's disease: a comparative study. *Dis Colon Rectum* 2008; **51**: 858-867
17 **Kessler H**. Laparoscopic surgery in inflammatory bowel disease: is the future already here? *Curr Opin Gastroenterol* 2006; **22**: 391-395
18 **Marceau C**, Alves A, Ouaissi M, Bouhnik Y, Valleur P, Panis Y. Laparoscopic subtotal colectomy for acute or severe colitis complicating inflammatory bowel disease: a case-matched study in 88 patients. *Surgery* 2007; **141**: 640-644
19 **Bruce J**, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg* 2001; **88**: 1157-1168

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2011 November 27; 3(11): I
ISSN 1948-9366 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Surgery*

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

Manuela Santos, PhD, Associate Professor, Department of Medicine, University of Montreal, Montreal Cancer Institute, CRCHUM/Notre-Dame Hospital, Pavillon De Seve Y5625, 1560 Sherbrooke Est, Montreal, QC, H2L 4M1, Canada

Ned Abraham, MBBS, FRACS, FRCS, PhD, Coffs Colorectal and Capsule Endoscopy Centre, University of New South Wales, 187 Rose Avenue, PO Box 2244, Coffs Harbour, NSW 2450, Australia

Chien-Hung Chen, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University, College of Medicine, No. 7, Chung-Shan South Road, Taipei 100, Taiwan, China

Christian Max Schmidt, MD, PhD, MBA, FACS, Departments of Surgery and Biochemistry/Molecular Biology, Indiana University School of Medicine, 980 W Walnut St C522, Indianapolis, IN 46202, United States

Christian Max Schmidt, MD, PhD, MBA, FACS, Departments of Surgery and Biochemistry/Molecular Biology, Indiana University School of Medicine, 980 W Walnut St C522, Indianapolis, IN 46202, United States

Chapel Alain, PhD, Department of Men Radioprotection, Laboratory of Radio Pathology and Innovative Therapy, Institute of Nuclear Safety and radioprotection, PO Box 17, Far 92262, France

Marcus VM Valadao, MD, Instituto Nacional de Cancer, Hospital do Cancer Unidade I, Hc2., Rua do Equador 831, Santo Cristo, Rio de Janeiro 20220-410, RJ, Brazil

Stavros J Gourgiotis, MD, PhD, Department of Second Surgical, 401 General Army Hospital of Athens, 41 Zakinthinou Street, Papagou, Athens 15669, Greece

Helena M Isoniemi, MD, PhD, Professor, Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Box 263, Helsinki 00029-HUCH, Finland

Chen-Guo Ker, MD, PhD, Professor, Department of Surgery, Kaohsiung Medical University, No. 100, Tz-You 1st Rd, Kaohsiung, Taiwan, China

Adnan Narci, Professor, Department of Pediatric Surgery, Afyon Kocatepe University School of Medicine, Izmir Street, 7km, Afyonkarahisar 03200, Turkey

Douglas S Tyler, MD, Department of Surgery, Duke University Medical Center, Box 3118, Durham, NC 27710, United States

Marcelo AF Ribeiro, MD, PhD, TCBC, TCBCD, FACS, Department of Surgery, Santo Amaro University, Alameda Gregorio Bogossian Sobrinho, 80/155, Santana de Parnaiba, SP 06543-385, Brazil

Vollmar Brigitte, MD, Professor, Institute of Experimental Surgery, University of Rostock, Schillingallee 69a, Rostock 18057, Germany

Sukamal Saha, MD, FACS, FRCS, FICS, Department of Orthopedics, 3500 Calkins Rd, Suite A, Flint, MI 48532, United States

Gregory Peter Sergeant, MD, Department of General Surgery, University Hospital Leuven, Herestraat 49, Leuven B-3000, Belgium

Caroline S Verbeke, MD, PhD, Department of Histopathology, Bexley Wing Level 5 St James's University, Hospital Beckett Street, Leeds LS9 7TF, United Kingdom

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2011 November 27; 3(11): I
ISSN 1948-9366 (online)

Events Calendar 2011

January 15-19, 2011
EAES Advanced Laparoscopic GI Surgery Course, Cairo, Egypt

January 20-22, 2011
Gastrointestinal Cancers Symposium (ASCO GI), San Francisco, CA, United States

January 26-30, 2011
5th UK Alpine Liver and Pancreatic Surgery Meeting, Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy

February 01-03, 2011
6th Annual Academic Surgical Congress, Huntington Beach, CA, United States

February 21-26, 2011
Minimally Invasive Surgery Symposium 2011, The Grand America Hotel, Salt Lake City, Utah, United States

March 03-06, 2011
The Society of Surgical Oncology 63rd Annual Meeting, San Antonio, TX, United States

March 10-13, 2011
The American Hepato-Pancreato-Biliary Association Annual Meeting, Miami Beach, FL, United States

March 14-17, 2011
British Society for Gastroenterology Annual Meeting, International Convention Centre, Birmingham, United Kingdom

March 25-27, 2011
NZAGS Conference 2011 GI Surgery, New Plymouth, New Zealand

March 30-April 02, 2011
The Society of American Gastrointestinal and Endoscopic Surgeons 2011 Annual Meeting, San Antonio Convention Center, San Antonio, TX, United States

April 02-06, 2011
The American Association for Cancer Research 102nd Annual Meeting, Orlando, FL, United States

April 10-12, 2011
The American Association of Endocrine Surgeons 32nd Annual Meeting, Houston, TX, United States

April 14-16, 2011
The American Surgical Association 131st Annual Meeting, Boca Raton, FL, United States

May 07-10, 2011
Digestive Disease Week, Chicago, IL, United States

May 07-10, 2011
45th Annual Meeting of the Pancreas Club, Chicago, IL, United States

June 15-18, 2011
19th International Congress of the European Association for Endoscopic Surgery, in collaboration with and incorporating the 15th National Congress of the Italian Society of Endoscopic Surgery, Torino, Italy

September 10-14, 2011
International Congress of Endoscopy, Los Angeles, CA, United States

September 22-24, 2011
5th joint EAES and ESGE, European Workshop on NOTES, Frankfurt, Germany

September 23-25, 2011
The New England Surgical Society 92nd Annual Meeting, Breton Woods, NH, United States

September 23-27, 2011
ECCO-European Society for Medical Oncology Congress, Stockholm, Sweden

October 23-27, 2011
The American College of Surgeons 97th Annual Clinical Congress, San Francisco, CA, United States

November 02-05, 2011
American Pancreatic Association 42nd Annual Meeting, Chicago, IL, United States

November 13-16, 2011
The Western Surgical Association 119th Scientific Session, Tucson, AZ, United States

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2011 November 27; 3(11): I-V
ISSN 1948-9366 (online)

GENERAL INFORMATION

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 336 experts in gastrointestinal surgery from 35 countries.

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

Maximization of personal benefits

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

Aims and scope

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

Columns

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

Name of journal

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

Indexing/abstracting

PubMed Central, PubMed, Digital Object Identifer, and Directory of Open Access Journals.

Published by

Baishideng Publishing Group Co., Limited

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 from 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, *WJGS* 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, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of 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 copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the 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/1948-9366office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-9366/g_info_20100305152206.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjgs@wjgnet.com, or by telephone: +86-10-85381891. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

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

Title page

Title: Title should be less than 12 words.

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

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

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

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

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

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

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381891 Fax: +86-10-85381893

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

Abstract

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

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

Key words

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

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-9366/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

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

Notes in tables and illustrations

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

Acknowledgments

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

REFERENCES

Coding system

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

example, "From references[19,22-24], we know that...".

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

PMID and DOI

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

Style for journal references

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

Style for book references

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

Format

Journals

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

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

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

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

In press

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

Organization as author

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

Both personal authors and an organization as author

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

No author given

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

Volume with supplement

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

Issue with no volume

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

No volume or issue

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

Books

Personal author(s)

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

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-9366/g_info_20100312191949.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

Editorial: http://www.wjgnet.com/1948-9366/g_info_20100312190249.htm

Frontier: http://www.wjgnet.com/1948-9366/g_info_20100312190321.htm

Topic highlight: http://www.wjgnet.com/1948-9366/g_info_20100312190447.htm

Observation: http://www.wjgnet.com/1948-9366/g_info_20100312190550.htm

Guidelines for basic research: http://www.wjgnet.com/1948-9366/g_info_20100312190653.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-9366/g_info_20100312190758.htm

Review: http://www.wjgnet.com/1948-9366/g_info_20100312190907.htm

Original articles: http://www.wjgnet.com/1948-9366/g_info_20100312191047.htm

Brief articles: http://www.wjgnet.com/1948-9366/g_info_20100312191203.htm

Case report: http://www.wjgnet.com/1948-9366/g_info_20100312191328.htm

Letters to the editor: http://www.wjgnet.com/1948-9366/g_info_20100312191431.htm

Book reviews: http://www.wjgnet.com/1948-9366/g_info_20100312191548.htm

Guidelines: http://www.wjgnet.com/1948-9366/g_info_20100312191635.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJGS*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Gastrointestinal Surgery
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjgs@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-8538-1891
Fax: +86-10-8538-1893

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 or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/1948-9366/g_info_20100312191901.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/1948-9366/g_info_20100312191818.htm.

Proof of financial support

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

Links to documents related to the manuscript

WJGS will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

WJGS is an international, peer-reviewed, Open-Access, 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, 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. The related standards are as follows. Publication fee: 1300 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge..