ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2012 December 16; 4(12): 518-578

Baishideng Publishing Group
www.wjgnet.com

WJGE World Journal of Gastrointestinal Endoscopy

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

Editorial Board

2009-2013

The *World Journal of Gastrointestinal Endoscopy* Editorial Board consists of 400 members, representing a team of worldwide experts in gastrointestinal endoscopy. They are from 45 countries, including Australia (7), Austria (1), Belgium (6), Brazil (7), Canada (5), Chile (2), China (26), Croatia (2), Cuba (1), Czech Republic (3), Denmark (1), Ecuador (1), Egypt (1), Finland (2), France (10), Germany (27), Greece (11), Hungary (4), India (15), Iran (2), Ireland (2), Israel (6), Italy (37), Japan (62), Lebanon (1), Lithuania (1), Malaysia (2), Mexico (1), Netherlands (6), New Zealand (1), Norway (2), Pakistan (2), Poland (2), Portugal (5), Romania (2), Singapore (2), South Africa (1), South Korea (13), Spain (17), Sweden (3), Thailand (5), Turkey (8), United Arab Emirates (1), United Kingdom (15), and United States (69).

Czech Republic

Marcela Kopacova, *Hradec Kralove*
Michal Procke, *Prague*
Miroslav Zavoral, *Prague*

Denmark

Peter Bytzer, *Koege*

Ecuador

Carlos Robles-Medranda, *Portoviejo*

Egypt

Nabil Ali Gad El-Hak, *Mansoura*

Finland

Paulina Salminen, *Turku*
Lars Mikael Victorzon, *Vaasa*

France

Romain Coriat, *Paris*
Bernard G Dallemagne, *Strasbourg*
Gerard Jean Gay, *Vandoeuvre les Nancy*
Lesur Gilles, *Boulogne*
René Lambert, *Lyon*
Sylvain Manfredi, *Rennes*
Barthet Marc, *Marseille Cedex*
JF Rey, *Saint Laurent Du Var Cedex*
José Sahel, *Marseille*
Nathalie Salles, *Pessac*

Germany

Marcel Binnebösel, *Aachen*
P Born, *Munich*
Stefan von Delius, *München*
Dirk Domagk, *Muenster*
Christoph Eisenbach, *Heidelberg*
Ines Gockel, *Mainz*
Arthur Hoffman, *Mainz*
Georg FBA Kähler, *Mannheim*
Günter Kampf, *Hamburg*
Ralf Kiesslich, *Mainz*
Andreas Kirschniak, *Tübingen*
Oliver Pech, *Wiesbaden*
Michael Pietsch, *Mainz*
Andreas Probst, *Augsburg*
Andrea Riphaus, *Bochum*
Raphael Rosch, *Aachen*
Claus Schäfer, *Munich*
Hubert J Scheidbach, *Magdeburg*
Peter Schemmer, *Heidelberg*
Hans Scherübl, *Berlin*
Thomas W Spahn, *Schwerte*
Holger Sudhoff, *Bielefeld*
Jens Tischendorf, *Aachen*
Michael Vieth, *Bayreuth*
Jochen Wedemeyer, *Hannover*
Uwe Will, *Gera*

Greece

Georgios K Anagnostopoulos, *Athens*
Anna Eleftheriadou, *Rethymnon*
Dimitris K Iakovidis, *Lamia*
Dimitrios Kapetanos, *Thessaloniki*
John A Karagiannis, *Athens*
Stefanos Karagiannis, *Kifissia*
Spiros D Ladas, *Athens*
Konstantinos A Papadakis, *Heraklion*
George H Sakorafas, *Athens*
Elias Xirouchakis, *Areos*

Hungary

Pal Demeter, *Budapest*
Lujber László, *Pecs*
Peter Lakatos, *Budapest*
István Rácz, *Gyor*

India

Ramanathan S Bharathi, *Uttar Pradesh*
Devendra C Desai, *Mumbai*
Evan L Fogel, *Indianapolis*
Uday Chand Ghoshal, *Lucknow*
Chittor M Habibullah, *Andhra Pradesh*
Rakesh Kochhar, *Chandigarh*
Rakesh Kumar, *New Delhi*
Sri Prakash Misra, *Allahabad*
Sandeep Nijhawan, *Rajasthan*
Kaushal Kishor Prasad, *Chandigarh*
Surinder Singh Rana, *Chandigarh*
Muthukumaran Rangarajan, *Tamil Nadu*
D Nageshwar Reddy, *Hyderabad*
Omar Javed Shah, *Kashmir*
Virendra Singh, *Chandigarh*

Iran

Tahereh Falsafi, *Tehran*
Mohammad Rahnavardi, *Tehran*

Ireland

Colm Ó'Moráin, *Dublin*
Eamonn M Quigley, *Cork*

Israel

Simon Bar-Meir, *Ramat Gan*
Rami Eliakim, *Haifa*
Zvi Fireman, *Hadea*
Irina Hirsh, *Haifa*
Tiberiu Hershcovici, *Jerusalem*
Jesse Lachter, *Haifa*

Italy

Paola De Angelis, *Rome*
Paolo G Arcidiacono, *Milan*
Alberto Arezzo, *Torino*
Gabrio Bassotti, *San Sisto*
Giampaolo Bresci, *Pisa*
Carlo Calabrese, *Bologna*
Salvatore MA Campo, *Rome*
Federico Carpi, *Pisa*
Livio Cipolletta, *Torre del Greco*
Sandro Contini, *Parma*
Salvatore Cucchiara, *Rome*
Gabriele Curcio, *Palermo*
Luigi Familiari, *Cavalluccio*
Lorenzo Fuccio, *Bologna*
Giuseppe Galloro, *Napoli*
Giovanni B Gasbarrini, *Rome*
Carlo M Girelli, *Busto Arsizio*
Mauro Manno, *Baggiovara di Modena*
Hugo Martines, *Savona*
Gabriele Masselli, *Rome*
Emanuele Meroni, *Milan*
Andrea Moglia, *Pisa*
Raffaele Pezzilli, *Bologna*
Venerino Poletti , *Forlì*
Salvatore Pucciarelli, *Padova*
Franco Radaelli, *Como*
Marmo Riccardo, *Luigi Curto Polla*
Maria Elena Riccioni, *Rome*
Stefania Romano, *Naples*
Emanuele Rondonotti, *Milano*
Gianluca Rotondano, *Torre del Greco*
Vittorio Terruzzi, *Como*
Cristina Trovato, *Milano*
Antonio Tucci, *Bologna*
Maurizio Vecchi, *Milan*
Maurizio Ventrucci, *Bologna*

Japan

Mitsuhiro Asakuma, *Osaka*
Hiroki Endo, *Kanagawa*
Shotaro Enomoto, *Wakayama*
Kuang-I Fu, *Kashiwa*
Makoto Hashizume, *Fukuoka*
Toru Hiyama, *Higashihiroshima*
Akira Hokama, *Okinawa*
Akira Horiuchi, *Komagane*
Kinichi Hotta, *Nagano*
Atsushi Imagawa, *Kagawa*
Hiroo Imazu, *Tokyo*
Haruhiro Inoue, *Yokohama*
Ryu Ishihara, *Osaka*
Naoki Ishii, *Tokyo*
Hajime Isomoto, *Nagasaki*
Takao Itoi, *Tokyo*
Satoru Kakizaki, *Gunma*
Hiroshi Kakutani, *Tokyo*
Terumi Kamisawa, *Tokyo*
Yoshihide Kanno, *Sendai*
Mototsugu Kato, *Sapporo*
Takashi Kawai, *Tokyo*

Hirofumi Kawamoto, *Okayama*
Hiroto Kita, *Saitama*
Koga Komatsu, *Akita*
Hitoshi Kondo, *Sapporo*
Hiroaki Kubo, *Fukuoka*
Keiichiro Kume, *Kitakyusyu*
Iruru Maetani, *Tokyo*
Hiroto Miwa, *Hyogo*
Akihiro Mori, *Aichi*
Akihiro Mori, *Aichi*
Yoshihiro Moriwaki, *Yokohama*
Naoki Muguruma, *Tokushima*
Shinji Nishiwaki, *Gifu*
Ichiro Oda, *Tokyo*
Kazuichi Okazaki, *Osaka*
Yasuhiro Oono, *Chiba*
Taro Osada, *Tokyo*
Yutaka Saito, *Tokyo*
Yuzo Sakai, *Chiba*
Naoto Sakamoto, *Tokyo*
Nobuyuki Sakurazawa, *Tokyo*
Yasushi Sano, *Hyogo*
Tomoyuki Shibata, *Toyoake*
Takashi Shida, *Chiba*
Atsushi Sofuni, *Tokyo*
Kazuki Sumiyama, *Tokyo*
Nobumi Tagaya, *Tochigi*
Hirokazu Takahashi, *Yokohama*
Kyosuke Tanaka, *Mie*
Shinji Tanaka, *Hiroshima*
Gen Tohda, *Fukui*
Tomoyuki Tsujikawa, *Shiga*
Noriya Uedo, *Osaka*
Shuji Yamamoto, *Kyoto*
Takayuki Yamamoto, *Yokkaichi*
Hideo Yanai, *Yamaguchi*
Kenjiro Yasud, *Kyoto*
Naohisa Yoshida, *Kyoto*

Lebanon

Kassem A Barada, *Beirut*

Lithuania

Laimas Virginijus Jonaitis, *Kaunas*

Malaysia

Sanjiv Mahadeva, *Kuala Lumpur*
Sreenivasan Sasidharan, *Pulau Pinang*

Mexico

OT Teramoto-Matsubara, *México*

Netherlands

Marco Bruno, *Rotterdam*
Dirk Joan Gouma, *Amsterdam*
Iris Lansdorp-Vogelaar, *Rotterdam*
Chris JJ Mulder, *Amsterdam*
Vasileios Panteris, *Rotterdam*
Harald Erwin Vonkeman, *Enschede*

New Zealand

Michael PG Schultz, *Dunedin*

Norway

Magdy El-Salhy, *Stord*
Odd Helge Gilja, *Bergen*

Pakistan

Syed H Ali Shah, *Karachi*
Lubna Kamani, *Karachi*

Poland

Stanislaw A Hac, *Gdansk*
Maciej Michalik, *Pomorskie*

Portugal

Miguel T Coimbra, *Porto*
Marie I Cremers, *Setúbal*
Mário Dinis-Ribeiro, *Porto*
Pedro N Figueiredo, *Coimbra*
Rui MA da Silva, *Porto*

Romania

Mihai Ciocirlan, *Bucharest*
Lucian Negreanu, *Bucharest*

Singapore

Zhiwei Huang, *Singapore*
Surendra K Mantoo, *Singapore*

South Africa

Roland N Ndip, *Alice*

South Korea

Young-Tae Bak, *Seoul*
Dong Kyung Chang, *Seoul*
Youn-Seok Cho, *Uijeongbu*
Seong Woo Jeon, *Daegu*
Jong-Man Kang, *Seoul*
Yong Sung Kim, *Gyeonggi-do*
Hang Lak Lee, *Sungdonggu*
Suck-Ho Lee, *Cheonan*
Jong Ho Moon, *Bucheon*
Dong Kyun Park, *Incheon*
Dae Kyung Sohn, *Gyeonggi*
Jaekyu Sung, *Daejeon*
Si-Young Song, *Seoul*

Spain

Jose FN Aguilar, *Palma*
Adolfo P Blanco, *Asturias*
Andres Cardenas, *Barcelona*
Gloria Fernández-Esparrach, *Barcelona*
Jesús García-Cano, *Cuenca*
Angels Gines, *Barcelona*
Angel Lanas, *Zaragoza*
G Payeras Llodrá, *Madrid*
Alfredo José Lucendo, *Tomelloso*
Enrique F Perez-Cuadrado Martinez, *Murcia*
Luis Rabago, *Madrid*
Eduardo Redondo-Cerezo, *Cuenca*
Luis Rodrigo, *Oviedo*
Jaume Boix Valverde, *Badalona*
Josep Llach Vila, *Barcelona*
Santiago Vivas, *León*

Sweden

George Dafnis, *Eskilstuna*
Per-Ola Park, *Borås*
Carlos A Rubio, *Stockholm*

Thailand

Somchai Amornyotin, *Bangkok*
Thawatchai Akaraviputh, *Bangkok*
Udom Kachintorn, *Bangkok*
Varut Lohsiriwat, *Bangkok*
Rungsun Rerknimitr, *Bangkok*

Turkey

Selcuk Disibeyaz, *Nkara*
Mehmet Eken, *Istanbul*
Muammer Kara, *Ankara*
Taylan Kav, *Ankara*
Nevin Oruc, *İzmir*
Burhan Ozdil, *Adana*
Nurdan Ozmeric, *Emek Ankara*
Sema Zer Toros, *Istanbul*

United Arab Emirates

Margit Gabriele Muller, *Abu Dhabi*

United Kingdom

Basil J Ammori, *Manchester*
Simon HC Anderson, *London*
Adam D Farmer, *London*
Annette Fritscher-Ravens, *Landon*
Gianpiero Gravante, *Bristol*
Abdulzahra Hussain, *London*
United KV Kodogiannis, *London*
Seamus J Murphy, *Newry*
Perminder Phull, *Aberdeen*

WJGE

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 4 Number 12 December 16, 2012

World Journal of Gastrointestinal Endoscopy
Volume 4 Number 12 December 16, 2012

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITING
Editorial Board of *World Journal of Gastrointestinal Endoscopy*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080038
Fax: +86-10-85381893
E-mail: wjge@wjgnet.com
http://www.wjgnet.com

EDITORIAL OFFICE
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-85381893

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
December 16, 2012

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.518

World J Gastrointest Endosc 2012 December 16; 4(12): 518-525
ISSN 1948-5190 (online)

EDITORIAL

Endoscopy in screening for digestive cancer

René Lambert

René Lambert, World Health Organization International Agency for Research on Cancer, Screening Group, Lyon 69372, France
Author contributions: Lambert R contributed solely to this work.
Correspondence to: René Lambert, Professor, World Health Organization International Agency for Research on Cancer, Screening Group, 150 cours Albert Thomas, Lyon 69372, France. lambert@iarc.fr
Telephone: +33-4-72738499 Fax: +33-4-72738499
Received: August 30, 2011 Revised: November 12, 2012
Accepted: December 1, 2012
Published online: December 16, 2012

Abstract

The aim of this study is to describe the role of endoscopy in detection and treatment of neoplastic lesions of the digestive mucosa in asymptomatic persons. Esophageal squamous cell cancer occurs in relation to nutritional deficiency and alcohol or tobacco consumption. Esophageal adenocarcinoma develops in Barrett's esophagus, and stomach cancer in chronic gastric atrophy with *Helicobacter pylori* infection. Colorectal cancer is favoured by a high intake in calories, excess weight, low physical activity. In opportunistic or individual screening endoscopy is the primary detection procedure offered to an asymptomatic individual. In organized or mass screening proposed by National Health Authorities to a population, endoscopy is performed only in persons found positive to a filter selection test. The indications of primary upper gastrointestinal endoscopy and colonoscopy in opportunistic screening are increasingly developing over the world. Organized screening trials are proposed in some regions of China at high risk for esophageal cancer; the selection test is cytology of a balloon or sponge scrapping; they are proposed in Japan for stomach cancer with photofluorography as a selection test; and in Europe, America and Japan; for colorectal cancer with the fecal occult blood test as a selection test. Organized screening trials in a country require an evaluation: the benefit of the intervention assessed by its impact on incidence and on the 5 year survival for the concerned tumor site; in addition a number of bias interfering with the evaluation have to be controlled. Drawbacks of screening are in the morbidity of the diagnostic and treatment procedures and in overdetection of none clinically relevant lesions. The strategy of endoscopic screening applies to early cancer and to benign adenomatous precursors of adenocarcinoma. Diagnostic endoscopy is conducted in 2 steps: at first detection of an abnormal area through changes in relief, in color or in the course of superficial capillaries; then characterization of the morphology of the lesion according to the Paris classification and prediction of the risk of malignancy and depth of invasion, with the help of chromoscopy, magnification and image processing with neutrophil bactericidal index or FICE. Then treatment decision offers 3 options according to histologic prediction: abstention, endoscopic resection, surgery. The rigorous quality control of endoscopy will reduce the miss rate of lesions and the occurrence of interval cancer.

Key words: Esophagus; Stomach; Colon; Adenoma; Adenocarcinoma; Endoscopy; Screening

Peer reviewer: Naoki Muguruma, MD, PhD, Department of Gastroenterology and Oncology, the University of Tokushima Graduate School, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan

Lambert R. Endoscopy in screening for digestive cancer. *World J Gastrointest Endosc* 2012; 4(12): 518-525 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/518.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.518

INTRODUCTION

Digestive endoscopy gives access to the lumen of the esophagus and stomach with gastroscopes and to the lumen of the colorectum with flexible sigmoidoscopes

and colonoscopes. The objective of the present analysis is to describe the role of endoscopy in the detection and treatment of cancer arising in the mucosal surface of the digestive lumen. The worldwide global cancer burden for both sexes in 2008 was estimated in the IARC database globocan[1] at 12 600 000 new incident cases and 7 560 000 deaths. The cumulative numbers for esophago-gastric and colorectal cancers were 2 700 000, i.e., 21% of the global estimated figure, for annual incident cases and 1 700 000 for annual deaths (22%). Measured figures are shown in population based cancer registries[2-8], which are tabulated in cancer incidence in five continents[9], but in most countries only a fraction of the population is reported in those registries. For national cancer statistics the data are completed by other sources from hospital registries, statistics of medical insurance and civil registration files for birth and death. Annual incidence and mortality rates are expressed per 100 000 persons in the population of a country or region. The crude rates show the actual risk, also influenced by the distribution of age classes in the population because the average risk of cancer increases with aging. Comparisons of the risk between different countries are therefore based on age standardized rates (ASR) of incidence and mortality which refer to a single population model of age classes (world population in the year 1960). Survival is estimated from cancer registries with a follow-up of the cases after registration. The 5-year relative survival rate compares survival in cancer patients and in a similar population when the disease is not present.

THE RISK OF CANCER IN THE DIGESTIVE TRACT

Geographic variations in incidence

In 2008, in the IARC GLOBOCAN database[1] the respective worldwide ASR incidence rate/100 000 for esophageal, gastric and colorectal cancer was at 19.2, 19.8 and 20.4 for men and at 4.2, 9.1 and 14.7 for women which are exposed to a lower risk than men, particularly for esophago-gastric cancer. However there are considerable variations of the risk between geographic regions or countries, and in the near future an increased number of incident cases is expected. This temporal trend is in relation to the global aging of the population, particularly in developing countries.

Esophageal squamous cell cancer occurs in relation to nutritional deficiencies and a low socio-economic status, and to alcohol and tobacco consumption. The incidence is relatively low in North America and Europe. Some areas of China, South Africa (Transkei), South America, are exposed to a much higher risk. In Asia, areas of high risk include Iran, Northen India and China, where the ASR incidence in men and women is as high as 183.3 and 123.1/100 000 in Cinxian county in 1993-1997. In Western countries the incidence tends to lower since 20 years in relation to a decreased consumption of alcohol. The prognosis of this cancer is still very poor, with a 5-year relative survival as low as 12.3 % in the European Union in 1995-1999[5,6].

Esophageal adenocarcinoma develops in Barrett esophagus. The risk of malignancy in this columnar lined esophagus is now evaluated as 1 case per 200 years/patient. The incidence of this cancer is higher in North America and Northen Europe than in Asiatic countries. In cancer registries without histology subgroups, the incidence of adenocarcinoma is joined to that of squamous cell cancer. In registries with histology subgroups the proportion of adenocarcinoma varies with the regions[9]; the proportions are 59.5% in the white non hispanic population of the United States, 44.9% in Denmark, 53.0% in the Netherlands contrasting with 3.2% in Japan, 4.1% in France 3.9% in Brazil in 1988-1992. In the United States, during the period 1976-1987, the incidence of esophageal adenocarcinoma still increased[3] with an annual progression between 4% and 10%. Adenocarcinoma in esophagus is linked to the following factors: caucasian, male sex, old age, alcohol consumption, continuous smoking, dietary deficiency in fruit and vegetable, and a long history of reflux symptoms. The 5-year relative survival is low, in the range 25% to 30%, after surgical treatment.

Stomach cancer develops in the background of chronic atrophic gastritis in relation to *Helicobacter pylori* (*H. pylori*) infection[10-15]. The incidence is high in countries of Eastern Asia including Japan, in South America, much lower in North America and in Europa. In 1988-1992 the respective ASR incidence rate/100 000 for men and women was at 7.2 and 3.4 in the United States, 7.1 and 3.2 in Denmark, contrasting with high figures in Japan: (51.3 and 19.8 in Osaka registry) or in Chile: (43.1 and 16.0 in Valdivia registry). The recent worldwide decrease in incidence applies to the distal, but not to the proximal stomach. This temporal trend is attributed to changes in life style, diet and control of *H. pylori* infection. In Japan during period 1963-1989, the incidence decreased by 47% in men and 43% in women. In Western countries most cases are detected at advanced stage and the 5-year relative survival is low: in 2002-2004, its median value is 24.9 % in Europe and 25% in the United States. Detection occurs at an earlier stage in Japan and in 1987-1989, the 5-year survival is as high as 47% in the Osaka registry[4].

Colorectal cancer is more frequent in developed than in developing countries of the world. Favouring factors include a high intake in calories from meat and fat, excess weight and a low physical activity. In 1998-2002 the respective ASR incidence/100 000 for men and women is at 38.6 and 28.3 in the United States, 39.3 and 29.8 in Denmark and 37.4, and 21.7 in Japan. In Japan the incidence increases dramatically since 1975. In contrast in the United States the risk is stable since 1985, with a decline in mortality. The decrease in incidence is linked to the detection (and treatment) of premalignant neoplastic lesions during colonoscopy. The 5-year survival progressed in the United States, from 52.3% to 65.2% in men and from 52.3% to 66.3% in women during period 1975-2002

(3). In Japan it progressed from 37.1% to 71.7% in men and from 32.8 to 72.1% in women during period 1962-1996[4]. In the European Union the 5-year survival for both sexes, progressed from 54% in 1995-1999 to 56.8% in 2000-2002[5,6].

Precursors and premalignant lesions

The term of precursor applies to temporal ancestors of neoplasia like chronic inflammation and to premalignant neoplastic lesions which progress to cancer in successive stages of localized, regional, and distant invasion. In the digestive tract[16-25], cancer is called "superficial" when invasion is limited to mucosa and submucosa. The assessment of a precursor depends on histology and on molecular markers such as inactivation of the suppressor gene *TP53* encoding p53 protein, or the *CDKN2A* gene encoding P16; or amplification of *CCND1* encoding cyclin D1 protein or overexpression of proto-oncogenes like epidermal growth factor receptor or c-myc. The Vienna classification of neoplasia in the digestive mucosa[26,27] applies to superficial neoplastic lesions in the stomach and colon: group 1: negative for neoplasia; group 2: indefinite for neoplasia; group 3: low grade intraepithelial neoplasia; group 4: high grade intraepithelial neoplasia and intramucosal cancer; group 5: invasive cancer in the submucosa. The depth of invasion of a superficial cancer in the submucosa is measured by micrometry. The legitimacy of endoscopic resection is ensured up to 200 μm in esophagus, 500 μm in stomach and 1000 μm in colon. In addition, qualitative indices of poor prognosis are found in tumor grade, images of vascular invasion, and tumor budding.

For esophageal squamous cell cancer, chronic non erosive esophagitis which has a high prevalence in Henan, China, Transkei in Africa is classified as a precursor of neoplasia[21]. In contrast reflux esophagitis which is often erosive is not a precursor[19].

For esophageal adenocarcinoma, columnar metaplasia, with or without areas of intestinal metaplasia, is a precursor showing increased risk of development of neoplasia. Columnar metaplasia is linked to gastro-esophageal reflux; the surgical correction of reflux will not suppress the risk of cancer in the metaplastic segment of mucosa. The prevalence of columnar metaplasia in the adult population is estimated at 1.6% in Sweden[24].

For gastric cancer, atrophic gastritis with infection by *H. pylori* is considered as a precursor with increased risk of development of neoplasia. This risk is linked to achlorhydria and the possible direct oncogenic role of the bacteria, implanted in the epithelial cells[10,12]. The sequence leading from chronic gastritis to cancer has been described by Correa[16]. Pre-malignant neoplastic areas in the gastric mucosa are usually flat and the majority of polypoid lesions like the cystic polyps are not neoplastic.

For colorectal cancer chronic inflammation of the mucosa is a precursor and there is an increased risk of neoplasia in inflammatory bowel disease (IBD). In contrast most cases of cancer occur in absence of inflammation in the mucosa, through the sequence adenoma-carcinoma. Polypoid and non-polypoid adenomas are premalignant neoplastic lesions which develop through genetic alterations like APC inactivation, KRAS mutation and TP53 inactivation. Recently distinct genomic profiles have been established by DNA sequencing in colorectal carcinogenesis[28-30]: serrated lesions including hyperplastic polyps and sessile serrated lesions provide a common pathway between neoplastic and non-neoplastic precursors.

SCREENING FOR CANCER IN THE DIGESTIVE TRACT

Opportunistic and organized screening

When asymptomatic persons, at the individual scale, are the target of early detection of cancer, screening is called opportunistic; in this situation endoscopy, the primary procedure of detection, is included in an individual health contract between patient and doctor. When screening for cancer is adopted as a population based national policy, by the heath authorities of a country, the intervention is called organized or mass screening; then endoscopy is performed only in those persons positive to a relatively simple filter selection test. Actually there is no clear cut distinction between indications of endoscopy in organized or in opportunistic screening. Opportunistic screening by primary endoscopy, with free examination at regular intervals, may be offered by an industrial company, or by health care insurances or hospitals to their employees of affiliated persons. In this situation the screening is organized, but not population based. In the near future cancer screening should undergo a strategic revolution with the development of new selection tests prior to endoscopy. Stool and blood DNA tests based on epigenetics and nanotechnology, will be more easy to collect and have a larger spectrum, with enough sensitivity and specificity.

For squamous cell esophageal cancer early detection in opportunistic screening is based on upper gastrointestinal (GI) endoscopy in asymptomatic persons smoking and drinking alcohol. Organized screening trials are proposed to high risk populations in some areas of China exposed to a high risk and in Southern Brazil. The selection test is a balloon or sponge scrapping for cytology followed by upper GI endoscopy in positive cases.

For esophageal adenocarcinoma in columnar lined esophagus, the risk is too low to justify opportunistic or organized screening in asymptomatic persons, in the absence of reflux symptoms.

For stomach cancer, opportunistic screening with endoscopy is of current practice in persons asymptomatic or complaining from dyspepsia in regions of the world exposed to a high risk, particularly in Asia; Population based screening trials are occurring since 1963 in Japan[8,31-34]; the selection test is photofluorography with 7 small films, or the measure of the Pepsinogen I/Ⅱ ratio in the blood[32]. The filter test is followed by upper

GI endoscopy in positive cases. The prolonged policy of organized and opportunistic screening in this country resulted in a higher proportion of early gastric cancer and an increased 5-year survival.

For colorectal cancer, opportunistic endoscopic screening with flexible sigmoidoscopy or colonoscopy in asymptomatic persons from age 50-year, is of current practice in regions of Western countries exposed to a high risk. Organized and population based screening protocols are also proposed in in Europe, North America and in Japan. The fecal occult blood test (FOBT) is still the current selection test, either as a Guaiac FOBT or as a immunochemical test, like in Japan; this test requires only one stool sample and no specific diet. Various randomized trials on the efficacy of the FOBT test have been conducted[35-40]: (1) the American Minnesota trial, conducted in volunteers, with an annual rehydrated guaiac test, achieves a reduction in mortality in the screened group of 33%[37]. However the rate of positive tests is very high as well as the proportion of screened persons submitted to colonoscopy; and (2) the 2 European population based trials (Nottingham trial, Funen trial) based on a biennial non rehydrated test show a lower reduction is mortality in the screened group (15%-18%) but are more cost/effective because the proportion of colonoscopies is much lower[35,36]. The sensitivity of the FOBT trials to the detection of premalignant colorectal lesions is fairly low; therefore there is no impact on the incidence of cancer.

Evaluation of screening for cancer

Evaluation is not applicable to opportunistic screening at the individual scale. In contrast, evaluation of benefits, drawbacks, and cost/effectiveness, including follow-up of the results, is required for organized population based screening. The intervention is launched by the health authorities of a country in age classes exposed to the risk, from the age 50-year. Priority in evaluation of the benefit is given to the prevalence of the concerned cancer, screening is worthwhile only if there is a sizable impact on the health of the population. Aging persons are exposed to multiple concurrent causes of mortality. A life saved from digestive cancer is not saved from other diseases. Screening trials in age classes prone to cancer have an excessively high cost and a negligible impact on the global mortality of the population.

The benefit of a screening intervention with early detection of premalignant and malignant lesions is shown by the impact on the 5-year survival and mortality from the targeted tumor site. This impact is analyzed on death statistics and, in reference to stage and treatment, in cancer registries.

The harms and drawbacks of screening are as follows: (1) the intervention has an impact on morbidity with the potential complications of endoscopy; and (2) the number of cases detected and their mortality is artificially increased as compared to data in cancer registries because some of the detected cases would not be the final cause of death. This factor is well acknowledged for the screening of prostate cancer with the PSA antigen.

Multiple interfering bias must be accounted for, in the evaluation: (1) the lead time bias applies to cancer detected at an early preclinical stage, then the length of the survival is prolonged by definition; (2) the selection bias applies to cases detected during the first years of the intervention; these cases usually have a slow evolution and better prognosis; and (3) the stage migration bias refers to progress in early detection of cancer occurring along the years and independently from the screening intervention. Similarly the progress in treatment improves the results and increases artificially the impact of the intervention on mortality and 5-year survival, this is why randomized trials are required.

ENDOSCOPY IN DIAGNOSIS OF CANCER

Strategy of endoscopic diagnosis

Nowaday the basic material used in the endoscopy unit fulfills the following requirements: a recent model of electronic video-endoscope in the HDTV standard with an adapted processor and monitor-availability of image magnification either with an optical or electronic zoom or an adaptative focal in the objective-a technique of image processing, of which neutrophil bactericidal index is the more reliable. Chromoscopy is often used during the step of detection, indigo carmine being the most frequent dye. In agreement with the Japanese school, endoscopic diagnosis is based on two successive steps of detection and characterization[41,42] with prediction of histology and staging of depth of invasion in order to adopt treatment decision between 3 categories: (1) abstention in non-neoplastic lesions; (2) endoscopic resection in neoplastic lesions fulfilling the criteria of complete cure; and (3) surgical treatment.when those criteria are not ensured.

Detection of an abnormal area in the mucosa requires a complete cleanliness of the lumen in upper GI endoscopy as well as in colonoscopy, abnormal areas are first detected in standard vision on any of the following criteria: (1) obvious elevation or depression; (2) mucosal discoloration; and (3) interruption in the course of superficial capillaries. Nonpolypoid lesions, even large, can be missed when the operator lacks cognitive knowledge and training for a slight change in the color of the mucosa[41]. Exploration of the proximal colon requires a special attention, because poorly visible and flat lesions are more frequent and often covered with mucus. Chromoscopy is then used with indigocarmine, a non absorbable dye at 0.5% dilution, or absorbable dyes like crystal violet (0.2%) or methylene blue (0.5%). The lesion is classified in size as diminutive (up to 5 mm), small or intermediate (5 to 9 mm), or large (10 mm and more). Lesions with a superficial appearance are classified in the categories of type 0 of the Paris classification[43]: (1) subtype 0-1, polypoid or sessile (0-1p, 0-1s); (2) 0-2 non-polypoid with variants elevated (0-2a) flat (0-2b) or depressed (0-2c); and (3) 0-3 ulcerated. These categories have a distinct prognostic

value; depressed lesions, even small have a higher risk of malignancy than elevated lesions. In Japanese series the proportion of non-polypoid (0-1p) lesions is 84% in esophagus, 95% in stomach and 49% in colon.

Characterization follows detection and predicts the risk of malignancy. Prediction is based on morphologic subtype and on the microarchitecture, explored in magnification, with or without chromoscopy, and image processing[44-48]. The microarchitecture of the epithelium (pits grooves and crests) is called "pit pattern"; that of the superficial subepithelial capillaries is called "vascular pattern". The prediction of massive invasion in the submucosa from the pit pattern and the vascular pattern is a contra-indication to endoscopic treatment.

Morphology of neoplastic lesions in the digestive tract

In the esophagus, most superficial type 0 lesions in squamous cell cancer are flat or depressed. In a metanalysis of 143 centres in Japan the distribution of subtypes was: 2.2% in 0-1, 12.6% in 0-2a, 31.4% in 0-2b, 53% in 0-2c and less 1% in 0-3 (in 43). In magnifying endoscopy the vascular pattern of the normal squamous epithelium is distributed in regular intrapapillary capillary loops (IPCL). At a very early stage of neoplasia the IPCL are elongated; later they disappear with development of irregular vessels with a large diameter. For type 0 adenocarcinoma developed in the columnar lined esophagus the non-polypoid morphology is also predominant. In magnifying endoscopy the pit pattern of neoplastic areas shows an abrupt change in size of epithelial crests, which are irregular and distorted or an amorphous surface suggesting submucosal invasion. The alterations of the vascular pattern also relate to the depth of invasion in the columnar epithelium. Both histological types of cancer in the esophagus vary in morphology and in the time trends of incidence in various countries[49].

In the stomach the usual morphology of superficial neoplasia is non polypoid. Lesions flat or depressed are detected as discoloured areas (pale or red). Flat neoplastic lesions are easily missed during gastroscopy: A recent analysis of the miss rate for early gastric cancer has been conducted in Japan in the Fukui registry, cross referenced with databases on gastroscopy: the sensitivity of this procedure for gastric cancer was 81% with 19% false negative[33]. In the stomach most polypoid lesions correspond to non-neoplastic fundic cystic polyps or hyperplastic polyps. In magnifying endoscopy the normal pattern of regular round pits in the mucosa of the gastric fundus is replaced by a gyrus and villous pattern with irregular epithelial crests. An amorphous surface pattern suggests submucosal invasion. Concerning the vascular pattern in the gastric fundus, the honeycomb network of capillaries around the neck of gastric pits is replaced by abnormal vessels with a mesh, coil or corkscrew appearance. In the antrum the coiled subepithelial capillaries around epithelial crests are replaced by irregular and large vessels.

In the colon and rectum, the upward growth of adenomas results in polypoid type 0-1 neoplastic lesions. Polyps over 10 mm in diameter, are called advanced adenomas, Non-polypoid adenomas are classified as 0-Ⅱa. Depressed adenomas account for only 5% of neoplastic lesions, but invasion of the submucosa is frequent: the proportion reaches 35.9% in 0-2c lesions in a large series (n = 25 862) collected in Akita and Yokohama and 27% in another series[28,29] collected in Hiroshima. Laterally spreading tumors are large lesions, either granular or non-granular with an often depressed morphology. Sessile serrated lesions are non-neoplastic lesions, also large, over 10 mm, with a predominant lateral growth pattern; which have a significant risk of progression to serrated adenomas. Finally the majority of non neoplastic hyperplastic polyps are classified as non-polypoid 0-2a. In magnifying endoscopy the pit pattern of the colonic mucosa is described in categories: (1) type 1, normal, with small and regular pit opening; (2) type 2 with less contrasted pit openings for non-neoplastic hyperplastic lesions; (3) types 3l, 3s, 4, 5i, 5n for neoplasia with progression of irregularity of epithelial rests and branching from low to high risk of malignancy and submucosal massive invasion in type 5n. The vascular pattern is also classified in categories as faint, network; dense, irregular and sparse, the later suggesting submucosal invasion. The sensitivity of colonoscopy in the detection of colorectal cancer is superior to that of barium enema, with a higher proportion of Dukes-A stage among detected cases. Concerning premalignant adenomas the miss rate is high (27%) only for lesions, under 5 mm in diameter.

Endoscopic treatment of neoplastic lesions

After endoscopic diagnosis and prediction of the risk of malignancy of a lesion in the digestive mucosa with a superficial appearance there are 3 options in treatment decision: (1) non neoplastic lesions deserve no treatment, this applies to small hyperplastic polyps; (2) neoplastic lesions with prediction of curability by local treatment deserve endoscopic resection and "*en bloc*" resection is preferred. Lesions less than 25 mm are resected by endoscopic mucosal resection, lesions over 25 mm should be resected with submucosal dissection, by the endoscopic submucosal dissection technique. The curability of malignant neoplastic lesions developed in the squamous epithelium of the esophagus by endoscopic resection requires more severe criteria. Cure is ensured when the depth of tumor is intraepithelial (m1), micro-invasive (m2) and intramucosal (m3). When there is a superficial invasion of the submucosa (sm1) the risk of lymph node invasion is still acceptable for a local treatment. When invasion is deeper (sm2 and sm3), the risk reaches 40% and endoscopic resection should not be performed. In synthesis, histopathology of the specimen with serial sections is always required to confirm the legitimacy of the endoscopic treatment; and (3) neoplastic lesions without prediction of curability by local treatment deserve a surgical treatment. Decision on surgery is based on the depth of invasion in the submucosa and risk of lymph node invasion.

Endoscopy in screening and surveillance

Endoscopy has a major role in the detection and characterization of neoplastic lesions along the digestive tract in all screening strategies, as a primary procedure, applied to all screenies in opportunistic screening or after the selection of persons positive to a filter test in organized, population based, screening. Surveillance refers to endoscopy scheduled at regular intervals (2 to 5 years), independently of symptoms. It can be proposed to persons who are at increased risk of cancer because of specific environmental factors connected to life style, or to persons having a disease considered as a precursor of cancer. The endoscopic surveillance of the esophageal lumen is proposed to persons at risk of squamous cell cancer because of a high consumption of alcohol and tobacco. Surveillance is also proposed to persons in which a columnar lined esophagus has been detected when they are Caucasians, of male sex and are intensive smokers. The endoscopic surveillance of the gastric mucosa is proposed to patients with pernicious anemia and to those with chronic atrophic gastritis in the post operative stomach. The endoscopic surveillance of the colonic lumen is proposed to persons which were treated for adenomatous polyps or cancer[50,51] because new lesions may occur. It is also proposed to persons with IBD of continuous evolution. First degree relatives of persons who had a colorectal cancer are proposed a screening colonoscopy, followed by surveillance procedures if adenomas were detected.

Cost/effectiveness of endoscopy in screening

Cost/effectiveness (C/E) studies must be conducted in population based screening interventions conducted under the control of Health Authorities. The C/E ratio is estimated on the following criteria-cost per year of life gained in the population submitted to screening. The benchmark of the cost of a valid intervention is estimated at 40 000 $ per year of life gained in the concerned population. The evaluation takes in account the prevalence of the tumor in the population aged 50-year and over, and is based on modelization. The assumptions concern the efficacy of detection, dwelling time of premalignant lesions to malignancy, cost of procedures and treatment. With respect to digestive endoscopy the cost of procedures and treatment is limited to those performed in persons found positive to the selection test.

For esophageal cancer, there is no reliable analysis of the C/E ratio in screening for esophageal squamous cell cancer even in countries with a high risk, and organized screening is not recommended for esophageal adenocarcinoma.

For stomach cancer, in Japan organized population based screening is operational. The traditional filter test is the 7 films radiophotofluorography. Recent studies confirm the comparable validity of the Pepsinogen I/Ⅱ ratio as a filter test. In Western countries there is no population based screening, but many studies taking in account the frequency of the clinical symptoms of dyspepsia, have compared the costs of 2 distinct strategies of opportunistic screening in patients with dyspepsia: the prompt endoscopy strategy uses no filter test and upper GI endoscopy is the primary exploration. In contrast the so-called empirical strategy uses eradication of *H. pylori* as a filter test and upper GI endoscopy is proposed only if symptoms persist after the eradication. A randomized trial of the 2 strategies ended in higher cost of the empirical strategy.

For colorectal cancer the C/E ratio of organized and population based screening with FOBT as a filter test is well under the bench mark of a valid intervention, in the range 20 000 to 26 000 $ per life-year gained[40]. The following assumptions are adopted: (1) prevalence of premalignant polyps estimated at 30% in persons aged 50 years and over; (2) dwelling time of premalignant lesions to cancer estimated at 5 to 10 years-sensitivity of FOBT around 60% to cancer and 10% to polyps; (3) sensitivity of colonoscopy for neoplastic lesions 90%. Protocols wit the FOBT filter test before decision of colonoscopy have been compared to protocols based on primary flexible sigmoidoscopy or on primary colonoscopy. Depending on the strategy 3000 to 7000 life-years are gained for 100 000 persons screened at a cost of 250 to 1200 $ for persons submitted to endoscopy.

Primary colonoscopy for direct and opportunistic screening is progressively accepted in Western countries[52]. The C/E ratio depends on the compliance of population; on morbidity associated to test, on age range of the persons screened and on the intervals in surveillance endoscopy. The option-once in a life colonoscopy-is the most effective model and would cost around 750 $ per person screened. The option-colonoscopy every 10 years from age 50-years-is valid and cost/effective if the dwelling time from polyp to cancer is around 10 years. In such protocols the quality control of colonoscopy deserves extreme attention: Interval cancers occurring a few years after a false negative endoscopy have a disastrous impact on cost/effectiveness of the strategy[53-55].

Flexible sigmoidoscopy with a depth of insertion between 48-55 cm, can be used as a filter test in homogenous socio-economic groups rather than in population based mass screening[56]. The procedure is performed as well by GI specialized nurses; the potential of cancer detection is 40% to 60% of that of colonoscopy which is recommended in a second step, if a distal neoplastic lesion. Is found the Kaiser medical program conducted by Selby *et al*[57] a 50 % reduction in mortality from cancer in the distal colon and rectum was obtained. However in the absence of sentinel lesions in the distal colon, 20% to 30% of advanced neoplasia would be missed by sigmoidoscopy screening because only 30% of subjects with proximal neoplasia have an index distal colorectal lesion.

CONCLUSION

Endoscopic diagnosis, and eventually treatment, is the final step in screening asymptomatic persons for curable digestive cancer or premalignant precursors. Endoscopy

is the primary test in opportunistic screening and is also performed in organized population based screening in persons positive to the filter test, including false positive tests, Indicators of the quality of the endoscopic procedures are required because there is still a significant proportion of missed lesions, and interval cancers after false negative results. Organized and opportunistic screening are complementary in the detection of cancer in asymptomatic persons. In spite of being organized at a population scale, mass screening detects much less cases than opportunistic screening in individuals and in groups affiliated to industrial companies, Health Care Insurances or Hospitals. This difference was shown in Japan for gastric and colorectal cancer in the data published in the Journal of Gastroenterological mass survey. On the other hand the institution by National Health Authorities of a population based screening stimulates opportunistic screening in persons isolated or affiliated to groups.

REFERENCES

1 **Ferlay J**, Shin HR, Bray F. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon: IARC, 2010. Available from: URL: http://globocan.iarc.fr
2 Cancer Statistics in Japan 2005. Tokyo: National Cancer Center Tokyo, 2005
3 Surveillance Epidemiology and End Results. Bethesda: National Cancer Institute. Available from: URL: http:// seer.cancer.gov/
4 **Osaka Cancer Registry**. Survival of cancer patients in Osaka (1975-1989). Tokyo: Shinohara Publisher, 1998
5 **De Angelis R**, Francisci S, Baili P, Marchesi F, Roazzi P, Belot A, Crocetti E, Pury P, Knijn A, Coleman M, Capocaccia R. The EUROCARE-4 database on cancer survival in Europe: data standardisation, quality control and methods of statistical analysis. *Eur J Cancer* 2009; **45**: 909-930
6 **Verdecchia A**, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, Kunkler I. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol* 2007; **8**: 784-796
7 **Ajiki W**, Tsukuma H, Oshima A. Cancer incidence and incidence rates in Japan in 1999: estimates based on data from 11 population-based cancer registries. *Jpn J Clin Oncol* 2004; **34**: 352-356
8 A nationwide totalling of mass screening for gastrointestinal cancers in 2002 (in Japanese). *J Gastroenterol Mass Survey* 2005; **43**: 54-73
9 **Curado MP**, Edwards B, Shin HR, Storm H, Ferlay J, Heanu M, Boyle P. Cancer Incidence in Five Continents, Vol. IX. Lyon: IARC Scientific Publications, 2008
10 **Danesh J**. Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies. *Aliment Pharmacol Ther* 1999; **13**: 851-856
11 **Helicobacter and Cancer Collaborative Group**. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353
12 Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 1-241
13 **Muñoz N**, Vivas J, Buiatti E, Kato I, Oliver W. Chemoprevention trial on precancerous lesions of the stomach in Venezuela: summary of study design and baseline data. *IARC Sci Publ* 1996; (**139**): 125-133
14 **Parsonnet J**, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127-1131
15 **Webb PM**, Knight T, Greaves S, Wilson A, Newell DG, Elder J, Forman D. Relation between infection with Helicobacter pylori and living conditions in childhood: evidence for person to person transmission in early life. *BMJ* 1994; **308**: 750-753
16 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740
17 **Hsing AW**, Hansson LE, McLaughlin JK, Nyren O, Blot WJ, Ekbom A, Fraumeni JF. Pernicious anemia and subsequent cancer. A population-based cohort study. *Cancer* 1993; **71**: 745-750
18 **Kokkola A**, Sjöblom SM, Haapiainen R, Sipponen P, Puolakkainen P, Järvinen H. The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anaemia. A prospective follow-up study. *Scand J Gastroenterol* 1998; **33**: 88-92
19 **Lambert R**, Hainaut P, Parkin DM. Premalignant lesions of the esophagogastric mucosa. *Semin Oncol* 2004; **31**: 498-512
20 **Lambert R**, Parkin DM. Screening, Surveillance and Prevention of Gastric Cancer in Gastrointestinal Oncology. Philadelphia: Lippincott Williams & Wilkins, 2002: 341-354
21 **Muñoz N**, Crespi M, Grassi A, Qing WG, Qiong S, Cai LZ. Precursor lesions of oesophageal cancer in high-risk populations in Iran and China. *Lancet* 1982; **1**: 876-879
22 Paris Workshop on Columnar Metaplasia in the Esophagus and the Esophagogastric Junction, Paris, France, December 11-12 2004. *Endoscopy* 2005; **37**: 879-920
23 **Parkin DM**. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; **118**: 3030-3044
24 **Ronkainen J**, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Talley NJ, Agréus L. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology* 2005; **129**: 1825-1831
25 **Takubo K**, Vieth M, Aryal G, Honma N, Sawabe M, Arai T, Kammori M, Mafune K, Iwakiri K. Islands of squamous epithelium and their surrounding mucosa in columnar-lined esophagus: a pathognomonic feature of Barrett's esophagus? *Hum Pathol* 2005; **36**: 269-274
26 **Dixon MF**. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002; **51**: 130-131
27 **Schlemper RJ**, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, Sipponen P, Stolte M, Watanabe H, Takahashi H, Fujita R. Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. *Lancet* 1997; **349**: 1725-1729
28 **Kudo Se**, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Triadafilopoulos G, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Vieth M, Jass JR, Hurlstone PD. Nonpolypoid neoplastic lesions of the colorectal mucosa. *Gastrointest Endosc* 2008; **68**: S3-47
29 **Lambert R**, Kudo SE, Vieth M, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Jass JR, Triadafilopoulos G. Pragmatic classification of superficial neoplastic colorectal lesions. *Gastrointest Endosc* 2009; **70**: 1182-1199
30 **Jass JR**. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007; **50**: 113-130

31 **Lambert R**, Guilloux A, Oshima A, Pompe-Kirn V, Bray F, Parkin M, Ajiki W, Tsukuma H. Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. *Int J Cancer* 2002; **97**: 811-818

32 **Miki K**, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. *Am J Gastroenterol* 2003; **98**: 735-739

33 **Hosokawa O**, Tsuda S, Kidani E, Watanabe K, Tanigawa Y, Shirasaki S, Hayashi H, Hinoshita T. Diagnosis of gastric cancer up to three years after negative upper gastrointestinal endoscopy. *Endoscopy* 1998; **30**: 669-674

34 **Miki K**, Fujishiro M, Kodashima S, Yahagi N. Long-term results of gastric cancer screening using the serum pepsinogen test method among an asymptomatic middle-aged Japanese population. *Dig Endosc* 2009; **21**: 78-81

35 **Hardcastle JD**, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, James PD, Mangham CM. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; **348**: 1472-1477

36 **Maïmoun L**, Mariano-Goulart D, Couret I, Manetta J, Peruchon E, Micallef JP, Verdier R, Rossi M, Leroux JL. Effects of physical activities that induce moderate external loading on bone metabolism in male athletes. *J Sports Sci* 2004; **22**: 875-883

37 **Mandel JS**, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365-1371

38 **Mandel JS**, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, Snover DC, Schuman LM. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000; **343**: 1603-1607

39 **Ransohoff DF**. Colon cancer screening in 2005: status and challenges. *Gastroenterology* 2005; **128**: 1685-1695

40 **Wagner JL**, Tunis S, Brown M. Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young GP, Rozen P, Levin B, editors. Prevention and Early Detection of Colon Cancer. London; WB Saunders, 1996: 321-356

41 **Lambert R**, Jeannerod M, Rey JF. Eyes wide shut. *Endoscopy* 2004; **36**: 723-725

42 **Lambert R**, Saito H, Saito Y. High-resolution endoscopy and early gastrointestinal cancer...dawn in the East. *Endoscopy* 2007; **39**: 232-237

43 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43

44 **Kara MA**, Peters FP, Rosmolen WD, Krishnadath KK, ten Kate FJ, Fockens P, Bergman JJ. High-resolution endoscopy plus chromoendoscopy or narrow-band imaging in Barrett's esophagus: a prospective randomized crossover study. *Endoscopy* 2005; **37**: 929-936

45 **Kiesslich R**, Neurath MF. Chromo- and magnifying endoscopy for colorectal lesions. *Eur J Gastroenterol Hepatol* 2005; **17**: 793-801

46 **Kudo S**, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyuu A. Colorectal tumours and pit pattern. *J Clin Pathol* 1994; **47**: 880-885

47 **Kumagai Y**, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. *Endoscopy* 2002; **34**: 369-375

48 **Kuznetsov K**, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. *Endoscopy* 2006; **38**: 76-81

49 **Vizcaino AP**, Moreno V, Lambert R, Parkin DM. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. *Int J Cancer* 2002; **99**: 860-868

50 **Rex DK**, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, Burt RW, Byers T, Fletcher RH, Hyman N, Johnson D, Kirk L, Lieberman DA, Levin TR, O'Brien MJ, Simmang C, Thorson AG, Winawer SJ. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2006; **130**: 1865-1871

51 **Winawer SJ**, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, Smith RA, Lieberman DA, Burt RW, Levin TR, Bond JH, Brooks D, Byers T, Hyman N, Kirk L, Thorson A, Simmang C, Johnson D, Rex DK. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology* 2006; **130**: 1872-1885

52 **Lieberman DA**, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; **343**: 162-168

53 **Baxter NN**, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; **150**: 1-8

54 **Brenner H**, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst* 2010; **102**: 89-95

55 **Imperiale TF**, Glowinski EA, Lin-Cooper C, Larkin GN, Rogge JD, Ransohoff DF. Five-year risk of colorectal neoplasia after negative screening colonoscopy. *N Engl J Med* 2008; **359**: 1218-1224

56 **Atkin WS**. Flexible sigmoidoscopy as a mass screening tool. *Eur J Gastroenterol Hepatol* 1998; **10**: 219-223

57 **Selby JV**, Friedman GD, Quesenberry CP, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992; **326**: 653-657

S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.526

World J Gastrointest Endosc 2012 December 16; 4(12): 526-531
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

David M Friedel, MD, Associate Professor, *Series Editor*

Endoscopist's approach to nutrition in the patient with pancreatitis

Shahzad Iqbal, Jay P Babich, James H Grendell, David M Friedel

Shahzad Iqbal, Jay P Babich, James H Grendell, David M Friedel, Department of Medicine, Division of Gastroenterology, Winthrop University Hospital, Mineola, NY 11501, United States
Author contributions: Iqbal S and Babich JP wrote the paper; Grendell JH and Friedel DM reviewed the paper.
Correspondence to: Shahzad Iqbal, MD, Department of Medicine, Division of Gastroenterology, Winthrop University Hospital, 222 Station Plaza North, Suite 428, Mineola, NY 11501, United States. siqbal@winthrop.org
Telephone: +1-516-6632066 Fax: +1-516-6634617
Received: June 2, 2012 Revised: November 10, 2012
Accepted: December 1, 2012
Published online: December 16, 2012

Abstract

Nutritional therapy has an important role in the management of patient with severe acute pancreatitis. This article reviews the endoscopist's approach to manage nutrition in such cases. Enteral feeding has been clearly validated as the preferred route of feeding, and should be started early on admission. Parenteral nutrition should be reserved for patients with contraindications to enteral feeding such as small bowel obstruction. Moreover, nasogastric feeding is safe and as effective as nasojejunal feeding. If a prolonged course of enteral feeding (> 30 d) is required, endoscopic placement of feeding gastrostomy or jejunostomy tubes should be considered.

Key words: Acute pancreatitis; Nutrition; Enteral nutrition; Total parenteral nutrition; Nasoenteric tube feedings; Percutaneous endoscopic gastrostomy; Percutaneous endoscopic gastro-jejunostomy; Direct percutaneous endoscopic jejunostomy

Peer reviewers: Jiang-Fan Zhu, MD, Professor of surgery, Department of General Surgery, East Hospital of Tongji University, 150 Ji Mo Road, Pudong 200120, Shanghai, China; Vittorio Terruzzi, MD, Department of Gastroenterology, Ospedale Valduce, Via Dante, 11 22100 Como, Italy

Iqbal S, Babich JP, Grendell JH, Friedel DM. Endoscopist's approach to nutrition in the patient with pancreatitis. *World J Gastrointest Endosc* 2012; 4(12): 526-531 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/526.htm
DOI: http://dx.doi.org/10.4253/wjge.v4.i12.526

INTRODUCTION

One of the earliest references to the pancreas as a distinct organ occurs in the Talmud in which the organ is referred to as the finger of the liver[1]. Acute pancreatitis (AP) is an acute inflammatory disorder involving the pancreas, peripancreatic tissue, as well as adjacent organs. It has been estimated that in the United States there are more than 210 000 admissions yearly for AP with it being the third most common inpatient gastrointestinal diagnosis[2]. In the majority of patient it is a self-limiting disease and will usually resolve with five days of supportive management. Unfortunately, AP is severe in 10%-20% of cases and results in a systemic inflammatory response syndrome which predisposes the patient to multiple organ dysfunction and/or pancreatic necrosis. The overall mortality is reported as 10%-15%, ranging from < 5% to those presenting with mild AP to 20% with severe AP[3].

Nutritional therapy has an important role in the management of AP patients. In this review article, we will discuss the endoscopist's approach to manage nutrition in patients with AP. As mentioned before, AP resolves in majority of cases by supportive measures. Hence, it is important to know: When nutritional therapy is

required? Why it is important? And, how it should be given?

WHEN NUTRITIONAL THERAPY IS REQUIRED IN AP?

The majority of patients with mild AP respond to supportive care measures that form the hallmark of treatment in AP: bowel rest, intravenous hydration with crystalloid and analgesia. Oral intake is usually restored within 3-7 d of hospitalization once the patient is pain free in the absence of parenteral analgesia[4]. Supportive care with aggressive intravenous fluid replacement is of critical importance to counteract hypovolemia caused by third space losses, vomiting, diaphoresis, and greater vascular permeability caused by inflammatory mediators. There is abundant literature that has supported early aggressive fluid resuscitation in AP to improve the delivery of oxygen which in turn prevents or minimizes pancreatic necrosis and improves survival[4-6].

The nutritional support is needed in severe AP. Severe pancreatitis, defined by the Atlanta Symposium, is organ failure of at least one organ system (systolic blood pressure < 90 mm Hg, PaO_2 < 60 mmHg, creatinine > 2.0 mg/dL after rehydration, and gastrointestinal bleeding > 500 mL/24 h) and the presence of local complications such as necrosis, pseudocyst, and abscess[7]. When it is clear that the patient will not be able to tolerate oral feeding, nutritional support should be initiated.

WHY NUTRITIONAL THERAPY IS IMPORTANT IN SEVERE AP?

Severe AP is a hypermetabolic state with negative energy balance due to the release of hydrolytic enzymes, toxins, and cytokines[8,9]. Protein catabolism can increase by 80%, with negative nitrogen balance up to 20-40 g/d[10,11]. The mortality increases tenfold in patients unable to achieve a positive nitrogen balance[12]. Glucose intolerance develops in 40%-90% of cases due to insulin resistance and islet cell damage[13]. Hypocalcemia is noted in 40%-60% of patients, and is related to the severity of the disease. Micronutrient deficiencies can complicate the picture, especially in alcoholic pancreatitis[14,15]. Consequently, nutritional therapy has emerged from adjunctive therapy to proactive primary therapy in severe AP[16].

HOW NUTRITIONAL THERAPY SHOULD BE GIVEN IN SEVERE AP?

Approaches adopted for nutritional support in severe AP include; total parenteral nutrition, nasojejunal feeding, nasogastric feeding, or direct enteral feeding.

Total parenteral vs enteral nutrition

It is important to rest the pancreas in order to avoid further inflammation. All common routes of enteral nutrition stimulate the pancreas to some extent. Studies have shown that pancreatic stimulation can only be avoided by parenteral route only[17,18]. Parenteral nutrition used to be the standard route of nutrition support in severe AP[19]. However, several studies have shown that total parenteral nutrition (TPN) impair humoral and cell mediated immunity, increases the vigour of the proinflammatory response, increases bacterial translocation, and increases infection rate in various critically ill patients[20-23]. Enteral nutrition (EN) prevents bacterial translocation, is less expensive, and is associated with fewer complications than parenteral nutrition. The concept of EN in AP originated from a study by Voitk *et al*[24] in 1970s. The beneficial effects were noted in six patients with complicated AP in resolution of sepsis and achievement of positive nitrogen balance by jejunal feeding of an elemental diet. Since then, multiple controlled studies have reported the beneficial effects of EN over TPN in patient with severe AP.

McClave *et al*[25] performed one of the earliest prospective studies which compared the safety, efficacy, cost, and impact on patient outcome of early EN *vs* TPN in AP. Patients who were admitted with AP were randomized to receive EN *via* endoscopically placed nasojejunal feeding tube *vs* TPN within 48 h of admission. Thirty patients were studied over 32 admissions, 16 were given TPN and 16 EN. The mean cost of TPN per patient was over four times greater than that for EN. Compared with TPN, EN may promote more rapid resolution of the toxicity and stress response to pancreatitis.

In a smaller prospective study by Windsor *et al*[26], 34 patients with severe pancreatitis were randomized to receive either TPN or nasojejunal tube feeds. Despite unchanged pancreatic injury on computed tomography, clinical benefits were noted with enteral feeding in the form of faster reduction in C reactive protein (CRP) and APACHE II scores. Kalfarentzos *et al*[27] randomized 38 patients with severe pancreatitis to receive either TPN or nasoenteric tube feeding. The authors noted less morbidity, septic complications, and lower hospital costs with EN. In a study by Hernández-Aranda *et al*[28], 22 patient who had undergone emergent surgery for severe pancreatitis were randomized to TPN or surgically placed jejunostomy tube feedings. EN was associated with fewer septic complications and lower costs.

Abou-Assi *et al*[29] studied 156 patients with AP in a prospective randomized comparative trial between tube feeding and bowel rest with TPN. 75% of the patients improved with bowel rest, of the 53 remaining 26 were randomized to enteral nasojejunal tube feeds and the 27 to TPN. Duration of feeding was shorter with EN; metabolic and septic complications were higher in TPN-fed patients as were hospital costs. In another larger

Table 1 Enteral *vs* parenteral nutrition in the patient with acute pancreatitis

	Enteral nutrition	Parenteral nutrition
Advantages	Physiologic	Reliable and rapid delivery
	Less costly	Role for unstable patients
	Easier to implement	Use in face/neck/abdominal injury
	Preserves mucosal integrity	
	Less systemic infection	
Disadvantages	Diarrhea	Need for vascular device
	Tube migration/displacement	Hyperglycemia
	Bacteria colonization	Increased systemic infection
	Aspiration	Thrombophlebitis
	Gastric and abdominal distention	Small bowel mucosal atrophy

study, Petrov *et al*[30] randomized 70 patients with severe pancreatitis to receive either EN or TPN within 72 h of symptoms onset. Decreased incidence of infected pancreatic complications, multiple organ failure, and overall mortality was noted with EN.

A meta-analysis of randomized controlled trials comparing EN to TPN in AP was performed by Marik *et al*[31]. They concluded that EN should be the preferred route of nutritional support in patients with AP because it was associated with a significantly lower incidence of infection and a reduced length of hospital stay[31] (Table 1).

Methods of EN

The methods of delivering EN have evolved over the past millennium. There are reports that go as far back as the 15th century with the use of feeding tubes. In the 18th century, John Hunter, a pioneering British surgeon, used eel skin tubes for the purpose of EN[32]. These EN devices are usually delivered either *via* nasoenteric or direct enteral routes.

Nasoenteric feeding tubes

These are made of silicone or polyurethane, and they may be placed unassisted at the bedside or with endoscopic or fluoroscopic guidance. They range from 3.5F to 16F in diameter and 15 to 170 cm in length. Nasogastric feedings *vs* nasojejunal feedings has long been debated among experts as to which are the ideal approach. A major concern relates to stimulation of pancreatic secretion when feeding is introduced into the stomach or duodenum. There is evidence that intraduodenal feedings increase pancreatic enzymes synthesis and secretion, which may lead to an exacerbation of abdominal pain associated with a greater amylase level[33,34]. Nasojejunal placement overcomes the problem of gastroparesis, and any mechanical duodenal or gastric encroachment from pancreatic swelling or pseudocyst can be bypassed. Small bowel feeding increases energy delivery compared with gastric feeding. However nasojejunal feeding tube placement requires endoscopic placement, at times under fluoroscopic guidance and may require a suture or mechanical clip to anchor itself deep into the small intestine.

Nasogastric vs nasojejunal feeding

Nasogastric feeding can be advantageous as they are easier to place without a need for endoscopic assistance, and can even be placed by non-physician personnel. Multiple studies have been performed comparing nasogastric and nasojejunal feeding tubes.

Eatock *et al*[35] compared nasogastric with nasojejunal feeding that was introduced at 72 h from onset of pain in patients with AP. The study questioned whether or not early nasogastric feedings was as effective and safe as nasojejunal feeding in patients with severe AP. 49 consecutive patients with objectively graded severe AP were randomized to receive either nasogastric (27 patients) or nasojejunal (23 patients) feeding. The results demonstrated that nasogastric feeding was safe, with no differences in pain score, analgesic requirements, serum CRP or clinical outcome[35].

Kumar *et al*[36] compared early nasojejunal feeding to nasogastric feeding. A total of 31 patients with severe AP were randomized to receive feeding by either nasogastric (15 patients) or nasojejunal (16 patients) routes. The authors reported no difference in outcome measures (discharge, surgery, death) and satisfactory toleration of EN by both nasojejunal and nasogastric routes[36].

In a meta-analysis by Jiang *et al*[37] (articles 2-46), three randomized controlled trails including 131 patients with severe pancreatitis were reviewed. The authors concluded that early nasogastric enteral feed was as effective and safe as early nasojejunal enteral feed or TPN in acute severe pancreatitis, without increase in mortality. In another meta-analysis by Petrov *et al*[38], four studies on nasogastric tube feeding involving 92 patients with severe AP were analyzed. The enteral feeding was initiated within 24-72 h of admissions. The nasogastric enteral feeding was found to be safe and well tolerated in most of the patients with severe AP.

Direct enteral feeding

Sinusitis, tube malposition, aspiration, nasal trauma, and significant patient intolerance are amongst the difficulties with nasoenteric tubes[39]. Nasoenteric feeding is preferred for patients expected to resume oral feeding within 30 d (reference asge-enteral tubes articles)[40]. If a prolonged course of enteral feeding is required, endoscopic placement of feeding gastrostomy or jejunostomy tubes is indicated.

Percutaneous endoscopic gastrostomy (PEG) tube-is indicated for patients that cannot consume adequate nutrition but have a working gastrointestinal tract. The

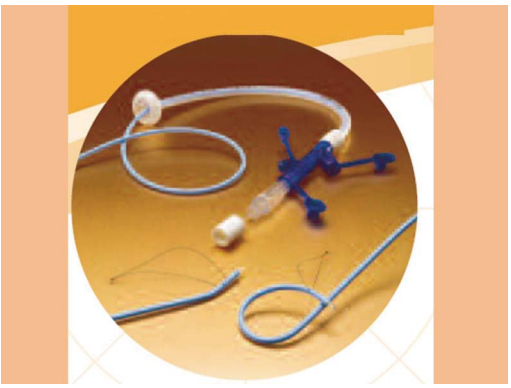

Figure 1 Percutaneous endoscopic gastro-jejunostomy through-the-percutaneous endoscopic gastrostomy jejunal feeding tube (Permission from Boston Scientific Natick, MA).

most common indications for PEG placements are dysphagia due to neurological causes, oropharyngeal or esophageal cancer, and severe facial trauma[41]. In patients with sequela of severe pancreatitis, such as pancreatic pseudocyst, necrosis, abscess that can be managed as an outpatient the endoscopic approach is ideal.

Percutaneous endoscopic gastro-jejunostomy (PEG-J)-is an option for patients who cannot tolerate gastric nutritional infusions, are at considerable risk for aspiration, and/or require gastric decompression and jejunal feeds. The PEG-J procedure as initially described involved passing a jejunal tube through a PEG, grasping the J-tube with an endoscopic forceps or snare, and advancing the scope and J-tube into the duodenum[42,43] (Figure 1).

Direct percutaneous endoscopic jejunostomy (DPEJ)-is a modification of PEG placement. The indications are the same as those of PEG-J, but also include post-surgical patients with anatomy precluding PEG[44,45]. A colonoscope is advanced through the mouth, into the jejunum and transillumination is performed. The procedure is complete as described for pull-type PEG placement. DPEJ is more difficult and time consuming to perform than PEG, and fluoroscopic guidance may be beneficial. Enteral formula infusion may begin immediately and adjusted to goal[46].

Timings for initiation of EN

Enteral feeding should be initiated shortly after admission with severe AP. Hegazi *et al*[47] studied early jejunal feeding and clinical outcomes in patients with severe AP. 31 patients were enrolled and underwent bedside placement of a nasojejunal feeding tube using transnasal endoscopy with jejunal guidewire deployment followed by introduction of a semi-elemental formula. This study demonstrated that early initiation of deep jejunal feeding in the intensive care unit was associated with reduced mortality in a cohort of patients with severe AP. Multiple randomized controlled trials of enteral *vs* parenteral nutrition in AP showed that initiation of EN within 48 h of admission was associated with better clinical outcomes[27,29,48,49]. However, a delay in initiation of enteral feeds may lead to prolonged ileums and reduced tolerance[50]. Low volume enteral feed *via* continuous low rate infusion can still be given in patients with significant ileums[19].

Initiation of oral feeding after severe AP

There is a paucity of data on the optimal timings or type of oral diet. Oral diet is usually initiated when abdominal pain or tenderness has subsided, there are no complications, and serum amylase and/or lipase levels are near normal[19]. A clear liquid diet is given first, followed by gradual advancement as tolerated to a diet rich in carbohydrates and protein but low in fat. The abdominal pain may recur, usually on day 2 or 3 of oral reseeding[51]. The risk factors are longer duration of initial pain (> 6 d), higher severity index on computed tomography scan, and higher serum lipase (> 3 times normal) the day before oral reseeding.

In conclusion, nutritional support is required in severe AP. It has emerged as a proactive primary therapy in such patients. Enteral feedings have been clearly validated as the preferred route for feeding patients with acute severe pancreatitis who require nutritional support. Parenteral nutrition is reserved only for patients who are intolerant of enteral feedings or have a contraindication to enteral feedings such as small bowel obstruction. EN should be initiated early (preferably within 48 h) of admission. Nasogastric feeding is safe and as effective as nasojejunal feeding. If a prolonged course of enteral feeding (usually over 30 d) is required, endoscopic placement of feeding gastrostomy or jejunostomy tubes should be considered.

REFERENCES

1 **Pitchumoni CS**. Development and Anatomy of the Pancreas. *Netters Gastroenterol* 2004; 592
2 **Swaroop VS**, Chari ST, Clain JE. Severe acute pancreatitis. *JAMA* 2004; **291**: 2865-2868
3 **Beckingham IJ**, Bornman PC. ABC of diseases of liver, pancreas, and biliary system. Acute pancreatitis. *BMJ* 2001; **322**: 595-598
4 **Banks PA**, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379-2400
5 **Strate T**, Mann O, Kleinhans H, Rusani S, Schneider C, Yekebas E, Freitag M, Standl T, Bloechle C, Izbicki JR. Microcirculatory function and tissue damage is improved after therapeutic injection of bovine hemoglobin in severe acute rodent pancreatitis. *Pancreas* 2005; **30**: 254-259
6 **Fisher JM**, Gardner TB. The "golden hours" of management in acute pancreatitis. *Am J Gastroenterol* 2012; **107**: 1146-1150
7 **Bradley EL**. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993; **128**: 586-590
8 **McClave SA**, Snider H, Owens N, Sexton LK. Clinical nutrition in pancreatitis. *Dig Dis Sci* 1997; **42**: 2035-2044

9 **Latifi R**, McIntosh JK, Dudrick SJ. Nutritional management of acute and chronic pancreatitis. *Surg Clin North Am* 1991; **71**: 579-595
10 **Dickerson RN**, Vehe KL, Mullen JL, Feurer ID. Resting energy expenditure in patients with pancreatitis. *Crit Care Med* 1991; **19**: 484-490
11 **Havala T**, Shronts E, Cerra F. Nutritional support in acute pancreatitis. *Gastroenterol Clin North Am* 1989; **18**: 525-542
12 **Sitzmann JV**, Steinborn PA, Zinner MJ, Cameron JL. Total parenteral nutrition and alternate energy substrates in treatment of severe acute pancreatitis. *Surg Gynecol Obstet* 1989; **168**: 311-317
13 **Pisters PW**, Ranson JH. Nutritional support for acute pancreatitis. *Surg Gynecol Obstet* 1992; **175**: 275-284
14 **Pitchumoni CS**, Agarwal N, Jain NK. Systemic complications of acute pancreatitis. *Am J Gastroenterol* 1988; **83**: 597-606
15 **Wilson C**, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. *Br J Surg* 1990; **77**: 1260-1264
16 **Abou-Assi S**, O'Keefe SJ. Nutrition support during acute pancreatitis. *Nutrition* 2002; **18**: 938-943
17 **O'Keefe SJ**, Lee RB, Anderson FP, Gennings C, Abou-Assi S, Clore J, Heuman D, Chey W. Physiological effects of enteral and parenteral feeding on pancreaticobiliary secretion in humans. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**: G27-G36
18 **O'keefe SJ**, Lee RB, Li J, Zhou W, Stoll B, Dang Q. Trypsin and splanchnic protein turnover during feeding and fasting in human subjects. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G213-G221
19 **Ong JP**, Fock KM. Nutritional support in acute pancreatitis. *J Dig Dis* 2012; **13**: 445-452
20 **Marik PE**, Pinsky M. Death by parenteral nutrition. *Intensive Care Med* 2003; **29**: 867-869
21 **O'Keefe SJD**, Abou-Assi SA, Lee RB. Elemental diets infused into the duodenum are more potent stimulants of pancreatic trypsin and lipase secretion than oral polymeric diets. *Gastroenterology* 2000; **118**:A-4149
22 **Robin AP**, Campbell R, Palani CK, Liu K, Donahue PE, Nyhus LM. Total parenteral nutrition during acute pancreatitis: clinical experience with 156 patients. *World J Surg* 1990; **14**: 572-579
23 **Klein S**, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P. Nutrition support in clinical practice: review of published data and recommendations for future research directions. National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. *JPEN J Parenter Enteral Nutr* 1997; **21**: 133-156
24 **Voitk A**, Brown RA, Echave V, McArdle AH, Gurd FN, Thompson AG. Use of an elemental diet in the treatment of complicated pancreatitis. *Am J Surg* 1973; **125**: 223-227
25 **McClave SA**, Greene LM, Snider HL, Makk LJ, Cheadle WG, Owens NA, Dukes LG, Goldsmith LJ. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. *JPEN J Parenter Enteral Nutr* 1997; **21**: 14-20
26 **Windsor AC**, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI, Welsh F, Guillou PJ, Reynolds JV. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998; **42**: 431-435
27 **Kalfarentzos F**, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg* 1997; **84**: 1665-1669
28 **Hernández-Aranda JC**, Gallo-Chico B, Ramírez-Barba EJ. [Nutritional support in severe acute pancreatitis. Controlled clinical trial]. *Nutr Hosp* 1996; **11**: 160-166
29 **Abou-Assi S**, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol* 2002; **97**: 2255-2262
30 **Petrov MS**, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral *vs* parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg* 2006; **23**: 336-344; discussion 344-345
31 **Marik PE**, Zaloga GP. Meta-analysis of parenteral nutrition *vs* enteral nutrition in patients with acute pancreatitis. *BMJ* 2004; **328**: 1407
32 **Randall HT**. Sixth annual Jonathan E. Rhoads lecture. Enteral nutrition: tube feeding in acute and chronic illness. *JPEN J Parenter Enteral Nutr* 1984; **8**: 113-136
33 **O'Keefe SJ**, Broderick T, Turner M, Stevens S, O'Keefe JS. Nutrition in the management of necrotizing pancreatitis. *Clin Gastroenterol Hepatol* 2003; **1**: 315-321
34 **Kaushik N**, Pietraszewski M, Holst JJ, O'Keefe SJ. Enteral feeding without pancreatic stimulation. *Pancreas* 2005; **31**: 353-359
35 **Eatock FC**, Brombacher GD, Steven A, Imrie CW, McKay CJ, Carter R. Nasogastric feeding in severe acute pancreatitis may be practical and safe. *Int J Pancreatol* 2000; **28**: 23-29
36 **Kumar A**, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol* 2006; **40**: 431-434
37 **Jiang K**, Chen XZ, Xia Q, Tang WF, Wang L. Early nasogastric enteral nutrition for severe acute pancreatitis: a systematic review. *World J Gastroenterol* 2007; **13**: 5253-5260
38 **Petrov MS**, Correia MI, Windsor JA. Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. *JOP* 2008; **9**: 440-448
39 **Thomson A**. Nutritional support in acute pancreatitis. *Curr Opin Clin Nutr Metab Care* 2008; **11**: 261-266
40 **Jain R**, Maple JT, Anderson MA, Appalaneni V, Ben-Menachem T, Decker GA, Fanelli RD, Fisher L, Fukami N, Ikenberry SO, Jue T, Khan K, Krinsky ML, Malpas P, Sharaf RN, Dominitz JA. The role of endoscopy in enteral feeding. *Gastrointest Endosc* 2011; **74**: 7-12
41 **DiSario JA**, Baskin WN, Brown RD, DeLegge MH, Fang JC, Ginsberg GG, McClave SA. Endoscopic approaches to enteral nutritional support. *Gastrointest Endosc* 2002; **55**: 901-908
42 **Ponsky JL**, Aszodi A. Percutaneous endoscopic jejunostomy. *Am J Gastroenterol* 1984; **79**: 113-116
43 **Gottfried EB**, Plumser AB. Endoscopic gastrojejunostomy: a technique to establish small bowel feeding without laparotomy. *Gastrointest Endosc* 1984; **30**: 355-357
44 **Del Piano M**, Ballarè M, Carmagnola S, Orsello M, Garello E, Pagliarulo M, Sartori M, Montino F. DPEJ placement in cases of PEG insertion failure. *Dig Liver Dis* 2008; **40**: 140-143
45 **Maple JT**, Petersen BT, Baron TH, Gostout CJ, Wong Kee Song LM, Buttar NS. Direct percutaneous endoscopic jejunostomy: outcomes in 307 consecutive attempts. *Am J Gastroenterol* 2005; **100**: 2681-2688
46 **DiSario JA**. Endoscopic approaches to enteral nutritional support. *Best Pract Res Clin Gastroenterol* 2006; **20**: 605-630
47 **Hegazi R**, Raina A, Graham T, Rolniak S, Centa P, Kandil H, O'Keefe SJ. Early jejunal feeding initiation and clinical outcomes in patients with severe acute pancreatitis. *JPEN J*

Parenter Enteral Nutr 2011; **35**: 91-96

48 **Gupta R**, Patel K, Calder PC, Yaqoob P, Primrose JN, Johnson CD. A randomised clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis (APACHE II > or =6). *Pancreatology* 2003; **3**: 406-413

49 **Oláh A**, Pardavi G, Belágyi T, Nagy A, Issekutz A, Mohamed GE. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition* 2002; **18**: 259-262

50 **Cravo M**, Camilo ME, Marques A, Pinto Correria J. Early tube feeding in acute pancreatitis: a prospective study. *Clin Nutr* 1989; **8**: 14

51 **Lévy P**, Heresbach D, Pariente EA, Boruchowicz A, Delcenserie R, Millat B, Moreau J, Le Bodic L, de Calan L, Barthet M, Sauvanet A, Bernades P. Frequency and risk factors of recurrent pain during refeeding in patients with acute pancreatitis: a multivariate multicentre prospective study of 116 patients. *Gut* 1997; **40**: 262-266

S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.532

World J Gastrointest Endosc 2012 December 16; 4(12): 532-544
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

Tarantino Ilaria, Assistant Professor, *Series Editor*

Endoscopic ultrasound fine needle aspiration: Technique and applications in clinical practice

Benjamin Tharian, Fotios Tsiopoulos, Nayana George, Salvatore Di Pietro, Fabia Attili, Alberto Larghi

Benjamin Tharian, Fotios Tsiopoulos, Nayana George, Salvatore Di Pietro, Fabia Attili, Alberto Larghi, Digestive Endoscopy Unit, Catholic University, 00168 Rome, Italy
Author contributions: Tharian B was the main contributing author to the write up and editing of the review article, including collection of references, review of the topic and the final version; Tsiopoulos F, George N, Di Pietro S and Attili F contributed to the article and editing; Larghi A contributed to overview of the article write up, revisions, contributed the pictures, charts and review of the final version.
Correspondence to: Alberto Larghi, MD, PhD, Digestive Endoscopy Unit, Catholic University, Largo A. Gemelli 8, 00168 Rome, Italy. albertolarghi@yahoo.it
Telephone: +39-6-35511515 Fax: +39-6-30156581
Received: October 14, 2011 Revised: November 9, 2012
Accepted: December 1, 2012
Published online: December 16, 2012

Abstract

Since its initial report in 1992, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has now been incorporated into the diagnostic and staging algorithm for the evaluation of benign and malignant diseases of the gastrointestinal tract and of adjacent organs. Its introduction constitutes a major breakthrough in the endoscopic field and has gradually transformed EUS from a pure imaging modality into a more interventional procedure. In addition, the possibility of collecting samples, providing a definitive cytological and/or histological evidence of the presence of malignancy, has strongly contributed to changing EUS from a subjective, highly operator dependant procedure into a more objective one. This article will review the instrumentation, technique and the most important clinical applications of EUS-FNA.

Key words: Endoscopic ultrasound; Equipment; Technique; Fine needle aspiration; Tru Cut biopsy; Procore needle; Staging

Peer reviewer: Stefanos Karagiannis, MD, PhD, Gastrointestinal and Liver Unit, General and Oncology Kifissia Hospital Agioi Anargiri', Kaliftaki 14564, Greece

Tharian B, Tsiopoulos F, George N, Di Pietro S, Attili F, Larghi A. Endoscopic ultrasound fine needle aspiration: Technique and applications in clinical practice. *World J Gastrointest Endosc* 2012; 4(12): 532-544 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/532.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.532

INTRODUCTION

Since its initial report by Henriksen *et al*[1], endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has now been incorporated into the diagnostic and staging algorithm for the evaluation of benign and malignant diseases of the gastrointestinal (GI) tract and of adjacent organs[2]. Its introduction constitutes a major breakthrough in the endoscopic field and has gradually transformed EUS from a pure imaging modality into a more interventional and lately therapeutic procedure. In addition, the possibility of collecting samples, providing a definitive cytological and/or histological evidence of the presence of malignancy, has strongly contributed to changing EUS from a subjective, highly operator dependant procedure into a more objective one.

In this article, we have done a critical appraisal of recent published literature and reviewed the instrumentation, technique and the most important clinical applications of EUS-FNA. The role of EUS in diagnosis and staging of esophageal, gastric, rectal cancers, subepithelial tumors, pancreatobiliary cancers, mediastinal cancers, lung and miscellaneous tumors has been dealt with. Despite the availability of advanced cross sectional imaging

like computed tomography (CT) and magnetic resonance imaging, EUS is still the gold standard for diagnosis and staging of various gastrointestinal cancers in particular of the pancreas, due to its high sensitivity and specificity and safe technique of acquiring tissue. We have not covered topics like general role of EUS in diagnosis of pancreatobiliary stone disease, chronic pancreatitis, autoimmune pancreatitis or in screening patients with a family history. We have also not dealt with the most challenging and exciting therapeutic aspect of EUS in stone disease, pseudocysts, celiac blocks and fine needle injection of tumors. We have tried to focus on the issues that have strongest evidence currently and also just mention the controversial topics like use of EUS post neoadjuvant chemotherapy.

EQUIPMENT AND ACCESSORIES

Curvilinear echoendoscopes

EUS-FNA is performed using curvilinear array echoendoscopes (CLA-EUS) that are produced by three leading manufacturers: Olympus (Olympus Medical Systems Inc., Tokyo, Japan), Pentax (Pentax, Tokyo, Japan) and Fujinon (Fujifilm Corp., Tokyo, Japan). CLA-EUS provide a plane of imaging parallel to the long axis of the endoscope, with the transducer placed on the tip of the echoendoscope and directed to provide ultrasound images along one aspect of the instrument. These features allow for tracing the needle from its exit from the tip of the echoendoscope to its entrance into the target lesion under real-time ultrasound guidance. The working channel must be at least 2.8 mm to accept the FNA needle and presents at its end located on the side of the scope an elevator that is able to make changes in the exit angle of the FNA needle to facilitate the targeting process. Curvilinear echoendoscopes with a larger working channel diameter (from 3.7 to 4.2 mm) to allow for the passage of larger devices, such as stent, are available and are used for interventions that are beyond the present discussion. Recently, a forward viewing EUS scope has become available, with the working channel placed on the tip of the scope that allows for accessories to exit with the axis parallel to the longitudinal axis of the scope[3,4]. As compared to the oblique view, the perpendicular approach would theoretically facilitate access, optimize precision, and maximize transfer of force to the target site.

FNA Needles

Needles for EUS-FNA are currently available in 3 sizes (19, 22 and 25 gauge) (Table 1). All the needles have a removable stylet and the more recently developed are equipped with an adjustable length sleeve or sheath to fit precisely to the length of the working channel of the EUS scope, which varies between the three different brands. The stylet could have either a sharp tip or a smooth one, the latter requiring the stylet to be pulled back few millimeters before performing the FNA. Finer needles are used to gather cytological specimens, while larger needle can be utilized when acquisition of a tissue specimen for histological examination can be more useful to reach the definitive diagnosis. For this purpose, specifically designed biopsy needles have been developed (Quick-core biopsy needle and ProCore needle, Cook Medical Inc., Bloomington, IN).

Table 1 Endoscopic ultrasound-guided fine needle aspiration needles

Manufacturer, model	Needle diameter (gauge)	Intended sample
Cook		
Echo-tip ultra	25, 22, 19G[1]	Aspirated cells
Quick-core	19G	Core biopsy
Procore	22, 19G	Core biopsy
Mediglobe		
Sonotip Ⅱ	25, 22, 19G	Aspirated cells
Olympus[2]		
Power-shot[3]	22G	Aspirated cells
EZ-shot	22G	Aspirated cells

[1]19G needle have been used to acquire core biopsy samples; [2]Compatible only with Olympus scopes; [3]Reusable. G: Gauge.

EUS-FNA TECHNIQUE

When available, EUS-FNA should be done under deep sedation with the assistance of an anesthesiologist. The FNA technique includes several phases: (1) Targeting of the lesion: The best position to perform EUS-FNA is with the target lesion in the center of the US image, adjacent to the transducer. Minimization of the distance between the target lesion and the tip of the EUS scope is made by using the up-down wheel of the scope. Color Doppler imaging should be then used to exclude the presence of interposing vessels; (2) Preparation of the needle: The needle-catheter assembly is passed through the working channel of the echoendoscope until the system handle locks in at the end of the biopsy channel. When necessary, the sheath is put forward in the working channel until its tip becomes visible on the ultrasound screen. The needle stop on the system handle is then unlocked to be ready to perform FNA; (3) Puncturing: Before advancing the needle, for some of the commercially available 19- and 25- gauge needles the stylet needs to be pulled out. When targeting lymph nodes important for staging of esophageal, gastric, and rectal cancers, attention should also be paid not to pass through an affected area of the wall of the GI tract under evaluation to avoid false positive results. The needle is then advanced under real-time EUS guidance into the middle part of the target lesion by using a quick, strong thrust of the handle. If the stylet has been pulled out as described above, it is necessary to push it all the way back to remove debris eventually collected. The stylet is then completely withdrawn and a 10-20 mL syringe attached to the end of the needle device; (4) Sample collection: Once inside the lesion, after applying negative pressure suction by opening the lock device of the syringe, the needle is moved back and forth 10 to 20 times under EUS guidance. The suction syringe is then released, the needle withdrawn into

the catheter, and the whole system removed from the echoendoscope; and (5) Specimen handling: The material in the FNA needle is obtained by pushing air from a syringe and it is placed on pre-labeled glass slides or into a container with Cytolit™ (Hologic-Cytyc Co, Marlborough, United States) to perform liquid-based cytology or a container with formalin for histological analysis or cell-block preparation. The use of one or the other technique varies from center to center.

The choice of the needle to be used depends on the type and site of the lesion to be sampled, whether the lesion is solid or cystic, and whether the access to the lesion can be difficult because of the angle or bend of the needle required to reach the target. Studies comparing 22- and 25-gauge needles have mainly been performed in patients with pancreatic masses with controversial results[5-8]. Most of these studies, however, were based on a small sample size, while the only one with a prospective, randomized design on a large patient population has found no significant difference between the two needles with respect to cellular yield and ability to obtain a diagnosis[7].

The use of the tru cut biopsy needle (TCB) may overcome some of the limitations of EUS-FNA permitting histological analysis and performance of immunostaining[9]. Studies with this device conducted on different patient populations have reported a diagnostic accuracy ranging from 61% to 84%[10-17]. No clear advantages of EUS-TCB over EUS-FNA have been demonstrated, even in patients with possible lymphomas and GI subepithelial tumors that have been considered a class IIa indication for the use of EUS-TCB[9], without definitive evidence of superiority[10,15,16,18-22]. Overall, EUS TCB may be useful as adjunctive technique used in tandem or as a rescue procedure after negative FNA. A new needle (ProCore needle, Cook Medical Inc., Bloomington, IN) to acquire histological samples has recently become available. Results from the first feasibility multicentric study have shown a very promising diagnostic accuracy with only one single needle pass performed.

Alternatively to EUS-TCB and the ProCore needle, a standard 19-gauge needle can be used to acquire tissue samples for histological examination as described by Yasuda *et al*[23], who investigated this technique in 104 patients with mediastinal and/or intra-abdominal lymphadenopathy of unknown origin. They found an overall diagnostic accuracy of 98% with an 88% chance of correct subtyping of lymphomas based on the World Health Organization classification. In a more recent study including patients in whom histology was deemed to be more appropriate than cytology to reach a definitive diagnosis, Larghi *et al*[24], reported a diagnostic accuracy of 93.2% by using a modification of the technique first described by Yasuda *et al*[23]. The technique was referred to as EUS-guided fine needle tissue acquisition (EUS-FNTA) to distinguish it from EUS-FNA.

The usefulness of suctioning while doing needle passes has been evaluated by Wallace *et al*[25] during EUS-FNA of lymph nodes and by Puri *et al*[26], during EUS-FNA of solid masses. In lymph nodes the use of suction was associated with an increase in the cellularity of the specimen with, however, worse quality because of excessive bloodiness, without improvement in the likelihood of obtaining a correct diagnosis[25]. On the contrary in solid masses, suction yielded a significantly higher sensitivity and negative predictive values despite the proportion of target cells was relatively similar between the suction and non-suction sampling techniques[26].

Traditionally, the stylet is reinserted into the needle before each pass to prevent sample contamination while traversing the digestive wall. Recent studies, however, have found no differences in sample quality, contamination rate, and in sensitivity for cancer detection regardless of whether the stylet was reinserted or not[27,28].

Higher accuracy rates are achieved with on-site cytopathology examination to assess specimen adequacy that, however, is not available in all centers and may increase the cost of the procedure[29,30]. In case the procedure is performed without the assistance of on-site cytopathology examination, the minimum number of needle passes that are recommended to achieve a good diagnostic accuracy are 5 to 7 for pancreatic solid masses and 3 for lymph nodes, liver and miscellaneous lesions[25,31-33].

CLINICAL APPLICATION OF EUS-FNA

The potential clinical role of EUS-FNA is evolving with various medical advances in oncology and molecular genetics. These help us not only in staging of tumors but also in the treatment and prognostication of the same, taking us to newer frontiers.

The foremost indications of EUS-FNA are in taking biopsies from N1/M1 nodes in esophageal malignancy, mediastinal lymphnodes (suspected lung tumor N2/3) and masses, pancreatic tumor, pancreatic cyst assessment, perirectal and retroperitoneal nodes/masses, left adrenal, left lobe of the liver and subepithelial lesions, just to elaborate a few instances[1,2]. The main ones are discussed at length in this review.

EUS-FNA is not done in situations when it is unlikely to alter the management of a cancer. In addition to the usual contraindications for any endoscopic procedure including severe bleeding diathesis and thrombocytopenia, EUS-FNA is not advocated when good views of the lesion are not obtained or when there is a blood vessel or tumor on the way to the target and or high risk of tumor seeding[1,2,9]. The various pitfalls of EUS-FNA include underdiagnosis of pancreatic malignancy in a background of chronic pancreatitis or in cystic lesions, misinterpretation of bowel wall smooth muscle cells as gastrointestinal stromal tumor (GIST) and overinterpretation of metastasis in contamination by normal gastrointestinal epithelium.

Overall complication rate of EUS-FNA is 0.5% to 3%[2,4]. Most of these can be avoided and rectified by careful sampling by the endoscopist with an on-site cytopathologist if available and immunocytochemistry in

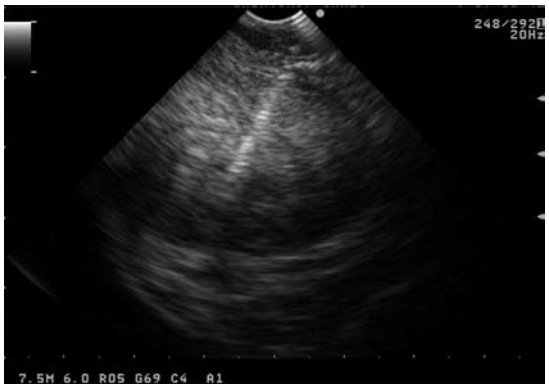

Figure 1 Endoscopic ultrasound-guided fine needle aspiration performed using the forward-viewing endoscopic ultrasound scope of a large perirectal lesion suspicious for rectal cancer recurrence.

addition to close clinical correlation and follow up.

Esophageal cancer staging

In esophageal cancer, once distant metastases to other organs have been ruled out by CT and/or FDG-pancreatic neuroendocrine tumor (PET), the choice between immediate surgery, neoadjuvant therapy followed by surgery or palliative treatment is mainly based on loco-regional staging. EUS-FNA may affect patient management by providing cytopathological confirmation of metastasis to regional and non-regional lymph nodes (mostly celiac) or to distant sites (Figure 1). The adjunct of EUS-FNA significantly improves EUS accuracy for lymph nodes staging as reported by a landmark study from the Mayo Clinic, in which a total of 125 patients with esophageal carcinoma were evaluated[34]. EUS-FNA proved to be more accurate than CT (87% *vs* 51%, $P < 0.001$) or EUS alone (87% *vs* 74%, $P = 0.012$) and to be able to significantly modify tumor stage determined by helical CT in 38% of patients (mostly towards a worse stage)[34]. This more accurate staging resulted in an increased rate of neoadjuvant treatments rather than direct surgery. This study, however, did not directly assess the impact of EUS-FNA on the overall patient management. The same group has subsequently proposed the possibility that the addition of more criteria to the standard four criteria to define malignant lymph nodes by EUS could result in a more selective use of FNA[35]. In particular, the use of six criteria permitted to avoid EUS-FNA in 42% of evaluated patients, a result that needs further confirmation before becoming standard practice.

Other studies have evaluated the clinical impact of EUS-FNA on patient management. EUS-FNA demonstration of distant lymph node metastases have been found to change the management strategy in 7% and 12% in one prospective and one retrospective study that involved an overall of 307 patients[36,37]. Moreover, small hepatic metastases and small metastatic pleural fluid collections undetected at previously performed CT have been discovered by EUS-FNA in 3% to 5% of patients with esophageal cancer[36,38]. Importantly, EUS-FNA can also be used to select the surgical approach to be used in patients with a resectable distal esophageal carcinoma and mediastinal LN visualized on EUS. EUS-FNA demonstration of positive mediastinal lymph nodes changed the management in 23% of the evaluated patients who underwent transthoracic esophagectomy, while those without proven involvement of the mediastinum underwent transhiatal resection that offers limited capability of lymph nodes removal[39].

The role of EUS-FNA after neoadjuvant chemoradiotherapy appears more limited in view of the significantly lower accuracy than that of integrated FDG-PET/CT (78% *vs* 93%; $P = 0.04$), which is also superior in predicting complete pathologic response[40].

Gastric cancer staging

Treatment options for gastric cancer strongly depend on tumor staging. It is well established that patients with early localized and those with metastatic disease should undergo surgery and palliation, respectively. On the other hand, in patients with a locally advanced cancer who cannot be resected for cure and in those who are potentially amenable to curative resection, neoadjuvant chemotherapy has proved to significantly improve prognosis[41]. Based on these new treatment paradigms, besides the degree of tumor infiltration, the exclusion of distant metastases and of loco-regional lymph node involvement is of paramount importance.

Data on the impact of EUS-FNA in patients with gastric cancer are limited. In a study by Mortensen *et al*[36], on 62 patients, EUS-FNA was performed in 12 patients (19.3%) for staging purposes. Overall, EUS-FNA demonstrated the presence of M1 disease in 8 patients and correctly excluded malignant ascites in another one, with an overall clinical impact in 14% of the studied cohort. The same group published two subsequent papers on 134 and 273 patients with gastric cancer, respectively, in whom staging was performed by combining endoscopic and laparoscopic ultrasound[42,43]. EUS-FNA was performed during the procedure if a positive (malignant) biopsy would have changed the patient's management. Unfortunately, data on the impact of EUS-FNA are not presented and cannot be extrapolated.

Recently, Hassan *et al*[44] studied the impact of EUS-FNA on the management of gastric cancer in 234 consecutive patients. EUS-FNA was performed in 81 patients (35%) in whom 99 lesions suspected for distant metastases were biopsied (78 were mediastinal lymph nodes). Overall 61 of these lesions in a total of 38 patients, mainly with tumor in the cardia, were found to be malignant. Excluding 4 patients in whom liver metastases were suspected but not verified by CT-guided FNA, in the remaining 34 patients these metastases were not seen or suspected by CT or other imaging modalities performed. As judged by the board of surgeons EUS-FNA changed the management in 34 of the 234 patients (15%) undergoing EUS for staging, avoiding unnecessary surgery[44].

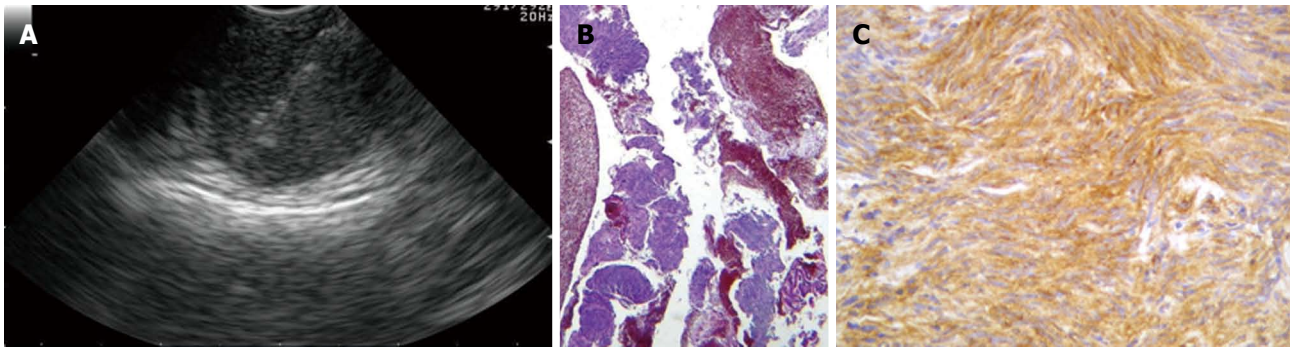

Figure 2 Subepithelial lesions. A: Endoscopic ultrasound-fine needle tissue acquisition of a subepithelial lesion using a 19 gauge needle; B, C: Histological examination showed large fragments of neoplastic tissue with solid structure, composed of regular, fused cells with mild atypia, which were intensively immunoreactivity for c-Kit, consistent with gastrointestinal stromal tumor.

Rectal cancer staging and diagnosis of extraluminal recurrence

EUS-FNA for rectal cancer has been evaluated for both lymph nodes staging and for detection of extraluminal recurrence. In the preoperative staging of rectal cancer, two studies have evaluated the clinical impact of EUS-FNA, with very similar results[45,46]. Both studies reported that EUS-FNA did not alter significantly the management as compared with EUS alone. In particular, Harewood *et al*[45] studied 80 patients and found that the addition of EUS-FNA did not change in all but one patient, what the surgeons would have done based on the results of EUS alone. Forty-one patients of the entire cohort underwent EUS-FNA of non-juxtatumoral lymph nodes detected during EUS examination and found that specificity and diagnostic accuracy of N staging by EUS alone or EUS-FNA were similar, with indeed a lower sensitivity of EUS-FNA (52% *vs* 74%). Shami *et al*[46] studied 60 patients of whom 48 underwent both CT and EUS. The authors found that EUS changed management in 38% of patients, while 16 patients identified as having non-juxtatumoral lymph nodes underwent EUS-FNA and the additional information obtained changed therapy in three (19%) of these patients, but only in 6% of the entire cohort[46]. It is possible that the lack of clinical impact of EUS-FNA in rectal cancer staging might be related to the close correlation between the T and N stages and to the fact that most perirectal lymph nodes detected at EUS during rectal cancer staging are malignant.

Differently, in patients evaluated for perirectal lesions suspicious for tumor recurrence (Figure 1), EUS-FNA has a strong clinical impact as demonstrated by the high diagnostic accuracy reported in 2 published studies[47,48]. In both series, EUS-FNA was significantly more accurate than EUS alone to diagnose malignant recurrence. Moreover, in the study with the largest patient population, EUS-FNA had a considerable impact on patient management in 26% of the cases.

Subepithelial lesions

The term subepithelial incorporates a variety of lesions including non-neoplastic lesions, as well as benign, premalignant, and overtly malignant neoplasms that are all located in the digestive wall beneath the epithelial layer. In this clinical setting, EUS-FNA has been used to overcome the limitation of the pure endosonographic inspection of these lesions, that can be useful to identify the layer of origin and formulate a differential diagnosis, but cannot differentiate benign and malignant conditions (Figure 2)[49]. Most of the studies have been performed on gastric lesions, which are represented predominantly by GISTs. EUS-FNA is able to gather representative material for cytopathological analysis in about 70%-84%[50-52], but often the material is insufficient to perform immunostaining, which are needed to distinguish GIST from other mesenchymal tumors. Moreover, the mitotic index that expresses the malignant potential of GISTs, cannot be reliably assessed on cytological specimens and even on tissue specimens acquired with the use of the tru cut needle[20,21].

This limits the usefulness of EUS-FNA and EUS-TCB for lesions in which the knowledge of the mitotic index is needed to guide further management (i.e., incidentally discovered asymptomatic lesions between 2 and 3 cm). On the other hand, in patients with a presumptive diagnosis of unresectable GIST in whom primary treatment with tyrosine kinase inhibitors is considered EUS-FNA or EUS-TCB confirmation of the diagnosis is required and they are likely to impact the management of these patients[53].

Pancreatic masses diagnosis and staging

Tissue diagnosis of pancreatic masses is one of the most important indications for EUS-FNA. Overall, EUS-FNA of pancreatic masses is safe[54], has a mean accuracy of about 85%[55], which can be increased with on-site cytopathology examination to assess specimen adequacy[29,30]. Two clinical scenarios need to be distinguished: (1) masses that are clearly unresectable on previous cross-sectional imaging studies from (2) masses that appear resectable. In the first case scenario a definitive diagnosis to guide further treatment is mandatory and should be obtained, when available, by EUS-FNA that is preferred to percutaneous image-guided tissue sampling (Figure

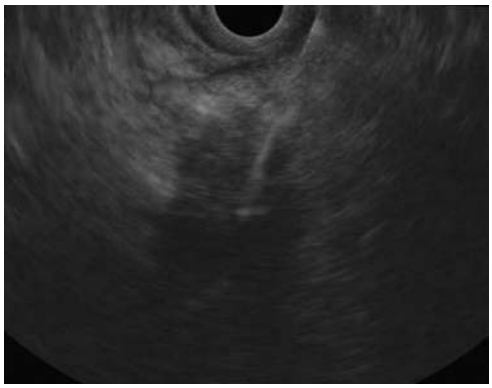

Figure 3 Endoscopic ultrasound-guided fine needle aspiration of a pancreatic mass of the uncinate process invading the superior mesenteric artery.

3)[56]. A recent single center, prospective, randomized, cross-over study has demonstrated EUS-FNA to be superior to US or CT-guided biopsy to determine the nature of pancreatic solid lesions[57]. EUS-FNA has also been found to be the most cost effective test for pancreatic adenocarcinoma when compared with CT-guided FNA and surgical diagnosis[58]. In addition, EUS-FNA can provide additional staging information, by sampling: (1) lymph node metastases in the celiac, lumboaortic, retroduodenopancreatic and superior mesenteric regions; (2) small hepatic lesions missed on CT[59]; and (3) small pocket of previously undetected ascites[60], all sites that when positive for malignancy indicate a poor prognosis for the patient[61]. Another important advantage of EUS-FNA over the percutaneous route is the lower risk of tumor seeding[62], and the potential to sample smaller lesions. On the other hand, the percutaneous route may be indicated in patients who are at risk for sedation-related complications and in those with surgically altered upper GI anatomy. When other biopsy techniques have failed, or in cases of previously done negative or inconclusive EUS-FNA, the use or the repetition of EUS-FNA is highly advised[63,64].

In potentially resectable pancreatic lesions, the argument for a definitive diagnosis before undergoing surgery is still debated[65]. Arguments made for EUS-FNA in potentially resectable lesions include an established protocol of preoperative neoadjuvant therapy, a demand by the patient for a conclusive diagnosis of cancer before consenting to surgery, and lastly to exclude unusual histology (lymphoma, acinar cell carcinoma, solid pseudopapillary tumor and pancreatic metastases) that can be found in up to 5% of individuals with pancreatic masses, who would not benefit from surgery[61,66]. The main argument against EUS-FNA in resectable lesions is that the performance of the procedure would not significantly affect further management, because a negative result cannot exclude the presence of malignancy due to its low negative predictive value[65]. Thus, the utility of EUS-FNA in this setting should be balanced with the potential risk of tumor seeding and varies among different centers.

A very important clinical challenge is the differentiation of pancreatic cancer from inflammatory masses due to focal chronic pancreatitis or autoimmune pancreatitis. A review of the performance of EUS-FNA for the differentiation of benign and malignant pancreatic masses, which included 25 studies with an overall of 4224 patients, found a median sensitivity of 83% (range 54%-95%), a median specificity of 100% (range 71%-100%), a median negative predictive value of 72% (range 16%-92%), and a median diagnostic accuracy of 88% (range 65%-96%)[65]. Definitions used to classify diagnostic cytology and the exclusion of non-diagnostic specimens in some studies may account for the wide ranges reported above. New techniques including contrast-enhanced EUS and elastosonoendosonography[67,68], DNA analysis[69], and K-ras mutation determination on FNA aspirates[70,71], have been tested to increase the possibility of differentiating cancer from focal chronic pancreatitis. If there is a high index of suspicion of autoimmune pancreatitis, tru cut biopsy needle may improve the diagnostic yield and can be used as a rescue procedure if conventional EUS-FNA has failed (100% *vs* 36%, $P = 0.0006$)[72]. When a pancreatic lymphoma is suspected by the clinical presentation, the use of flow cytometry significantly increases the diagnostic accuracy from 30.8% to 84.6% ($P = 0.01$)[73].

High sensitivity and diagnostic accuracy of EUS-FNA with immunocytochemical studies for PETs have been reported in two recent large retrospective cohorts of patients, including both functional and non-functional PETs (Figure 4)[74,75]. EUS-FNA helped to assess the malignant behavior of PETs and was able to predict 5-year survival after diagnosis[76]. Determination of Ki-67 expression on cytological specimens has still not gained widespread use due to the difficulty to obtain reproducible results and the availability of tissue biopsy specimens has been advocated[77,78].

Besides tissue diagnosis, studies aimed at directly assessing the clinical impact of EUS-FNA by demonstrating metastatic disease that would change the management of patients with pancreatic cancer are lacking. Mortensen *et al*[36] have performed the only study specifically designed to assess the impact of EUS-FNA in patients with pancreatic cancer. In 12 of 99 (12%) patients evaluated, EUS-FNA disclosed metastatic lymph nodes (6), liver lesions (4), malignant ascites (1), and retroperitoneal infiltration (1) that affected treatment decisions.

In the study by Spier *et al*[79] in Wisconsin on the predictors of pancreatic malignancy, they recommended close clinical follow up of patients suspected to have pancreatic cancer, with negative EUS-FNA, for at least 6 mo, since the FNA was not 100% reliable in ruling it out. This was more so in those individuals with vascular invasion or lymphadenopathy. Further they went on to say that further surveillance is not needed beyond 6 mo if there was no clinical or radiologic feature suggestive of malignancy[79].

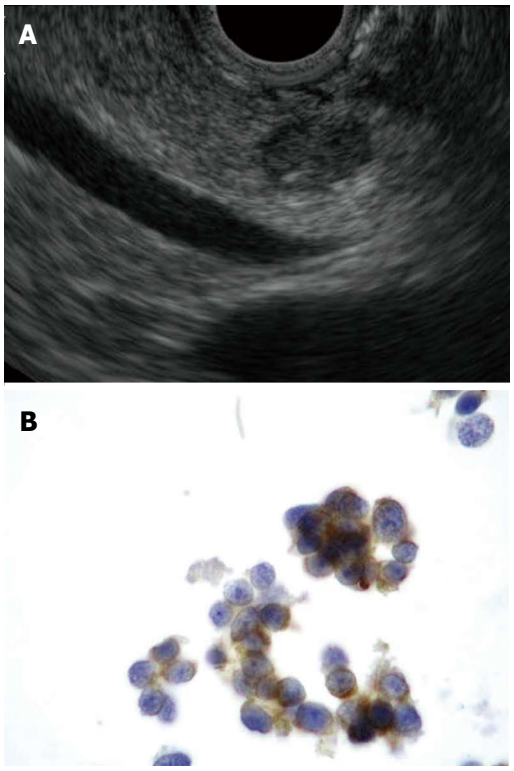

Figure 4 Pancreatic neuroendocrine tumors. A: Endoscopic ultrasound-guided fine needle aspiration of a small, hypoechoic, rounded, and well demarcated pancreatic body lesion; B: Diagnosed to be a neuroendocrine tumor by positive immunostaining for synaptophysin (thin layer cytology, 1000 ×).

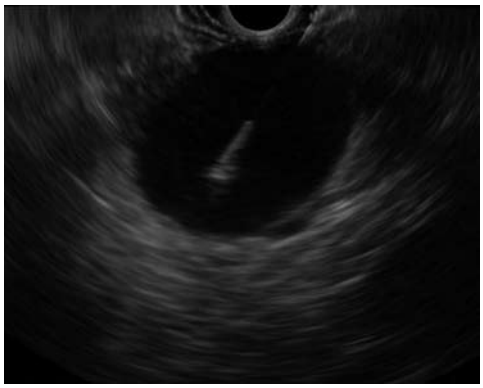

Figure 5 Endoscopic ultrasound-guided fine needle aspiration of a large pancreatic cystic lesion.

Table 2 Characteristics of pancreatic cystic lesions

	Cytology	Viscosity	Cyst CEA levels	Cyst amylase level
Serous cyst adenoma	Bland PAS+	Low	Low	Low
Mucinous cyst	Mucinous	Increased	High	Low
IPMN	Mucinous	High	High	High
Pseudocyst	Pigmented histiocytes	Low	Low	High

CEA: Carcinoembryonic antigen; IPMN: Intraductal papillary mucinous neoplasms.

Pancreatic cysts diagnosis

Pancreatic cysts encompass a wide spectrum of histological findings, including inflammatory pseudocysts, benign serous cystadenoma, and premalignant or malignant lesions, such as intraductal papillary mucinous neoplasms (IPMN), mucinous cystadenoma and cystadenocarcinoma. Because EUS imaging features are not sufficiently accurate to differentiate between mucinous and non-mucinous lesions and between benign and malignant IPMN, EUS-FNA has increasingly been used for the evaluation of pancreatic cysts (Figure 5)[80]. Cystic contents collected with EUS-FNA should be analyzed at least for cytology, amylase and carcinoembryonic antigen (CEA) (Table 2). The poor cellularity of the aspirated fluid limits the value of the cytologic examination in the distinction between mucinous and non-mucinous cysts. For this distinction, cystic fluid concentration of CEA has proved to be the most important test to identify mucinous lesions, despite considerable variation and overlapping in values[81]. CEA levels less than 5 ng/mL and greater than 800 ng/mL have been found in a pooled analysis of the published studies to be highly diagnostic for serous cystadenomas and mucinous lesions, respectively[82]. Determination of cyst amylase concentrations may help to further narrow the differential diagnosis, with high levels more frequently found in cysts that communicate with the main pancreatic duct (pseudocyst or IPMN), while values below 250 U/L virtually excludes a pancreatic pseudocyst[82]. The value of all of these analyses is limited by a relatively low sensitivity and by the fact that a minimum of 1 mL of liquid is required to perform the analysis, a task that is not feasible in lesions less than 1 cm in diameter.

A very high sensitivity and specificity of fluid analysis has been reached by using a combination of viscosity measurements, CEA and amylase levels[83]. Moreover, promising data on the use of cystic fluid DNA analysis in combination with CEA levels have been recently published[84,85], as well as the proteomic analysis of cyst fluid that could provide reliable candidates for developing new biomarkers for the preoperative management of pancreatic cysts[86]. Finally, the utilization of the tru cut needle and the echo brush to respectively acquire histological and cytological sample directly from the cystic wall appeared appealing, but their used is not widely accepted because of the potential risk of complications[87-89].

Bile duct tumors diagnosis and staging

Malignant bile duct tumors, cholangiocarcinomas, present as biliary strictures that need to be differentiated from strictures of benign origin. EUS FNA has been used in some centers as the second diagnostic modality in case of encoscopic retrograde cholangio-pancreatography failure[90-92]. In this clinical setting, EUS FNA has been found to have a sensitivity ranging from 43% to 86% for all biliary strictures and from 25% to 83% for those limited to the hilum[92]. Interestingly, preliminary results from

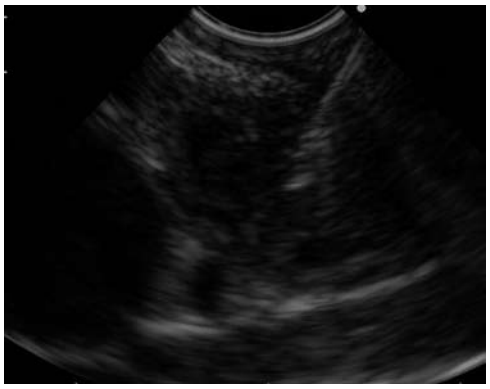

Figure 6 Endoscopic ultrasound-guided fine needle aspiration of a centimetric lesion causing a hilar biliary stricture performed using the forward viewing endoscopic ultrasound scope.

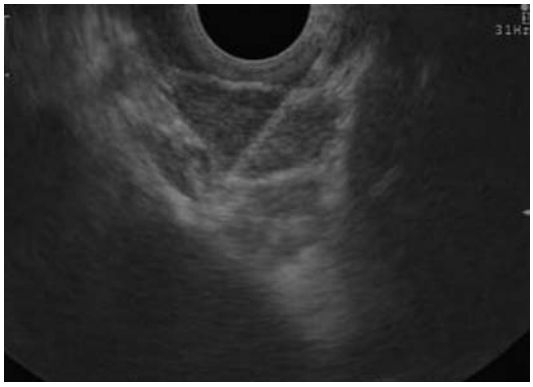

Figure 7 Endoscopic ultrasound-guided fine needle aspiration of lymph nodes in the aortic-pulmonary window in a patient with lung cancer.

an ongoing experience have used EUS FNA, performed with the newly developed forward viewing scope that seems to have some advantages over the conventional linear EUS scope for visualization of the hilar region, as a first diagnostic modality to guide further management decision in patients with hilar strictures (Figure 6)[93]. Finally, in patients with hilar tumors who are suitable for a multidisciplinary therapeutic approach recently developed at the Mayo Clinic including chemo-and radiation-therapy in association with liver transplantation[94], EUS-FNA of regional lymph nodes has a tremendous clinical impact in the selection of patients, avoiding unnecessary transplantation in about 20% of them[95].

Lung cancer diagnosis and staging

In patients with or suspected lung cancer established indications of EUS-FNA, which is able to access the posterior mediastinum (Figure 7), the paraesophageal lymph nodes, the left adrenal gland (Figure 8), and the liver, are either to obtain a definitive diagnosis by sampling centrally located lesions or mediastinal lymph nodes or to sample tissue from mediastinal lymph nodes and other locations in order to stage non-small cell lung cancer (NSCLC)[96]. Correct staging of NSCLC is important for rational allocation of patients to surgery, neoadjuvant

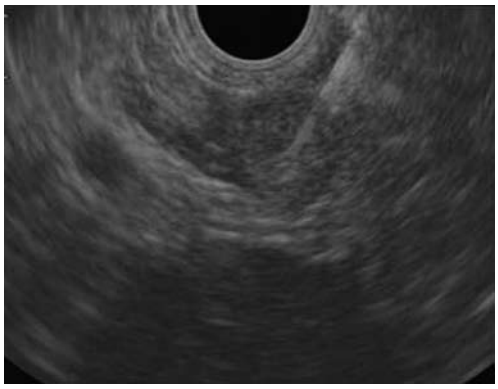

Figure 8 Endoscopic ultrasound-guided fine needle aspiration of a left adrenal mass in a patient with lung cancer.

or palliation therapy, whereas the current recommended treatment of small cell lung cancer involves chemotherapy and radiotherapy[97].

In patients with centrally located lesions after a previously non-diagnostic bronchoscopy, EUS-FNA has been found to have an extremely high diagnostic accuracy (97%) and may replace CT-guided biopsies and reduce the number of exploratory thoracotomies[98]. In view of the high sensitivity and specificity of EUS-FNA in the diagnosis of mediastinal lymph node metastases, as shown in two recently published large meta-analyses, the possible role of this technique as the first diagnostic test to be performed in patients with suspected lung cancer has also been evaluated[99]. Among 93 patients with a chest CT suspicious of lung cancer, EUS-FNA was able to establish tissue diagnosis in 70% of cases. Moreover, EUS-FNA was significantly better than CT at detecting distant metastases (accuracies of 97% and 89%, respectively; $P = 0.02$) and was able to detect small lymph node metastases (less than 1 cm) often missed by CT[99].

Several studies have clearly demonstrated the impact of EUS-FNA for staging of NSCLC. In patients with suspected or proven lung cancer and enlarged (> 1 cm) mediastinal lymph nodes on chest CT, EUS-FNA significantly reduces futile thoracotomies and prevents 66% of scheduled surgical procedures in these patients[100,101]. Regarding CT negative patients[102], EUS-FNA is able to detect advanced disease in 11% to 25% of cases, thus suggesting that it should be performed in all patients with NSCLC, irrespectively of the size of lymph nodes demonstrated by CT. EUS-FNA has also an important role in patients with a positive PET/CT to confirm or exclude the presence of mediastinal involvement[103,104], and the two methods should be seen as complementary[105]. On the other hand, patients without enlarged lymph nodes and a PET-negative mediastinum should proceed directly to surgery[106]. In addition, EUS-FNA should also be performed to provide tissue proof of left adrenal metastases in patients with enlarged or PET positive left adrenal gland[107].

EUS-FNA, however, cannot investigate the anterior mediastinum and cannot completely replace mediastinoscopy. Despite the fact that EUS-FNA can reduce

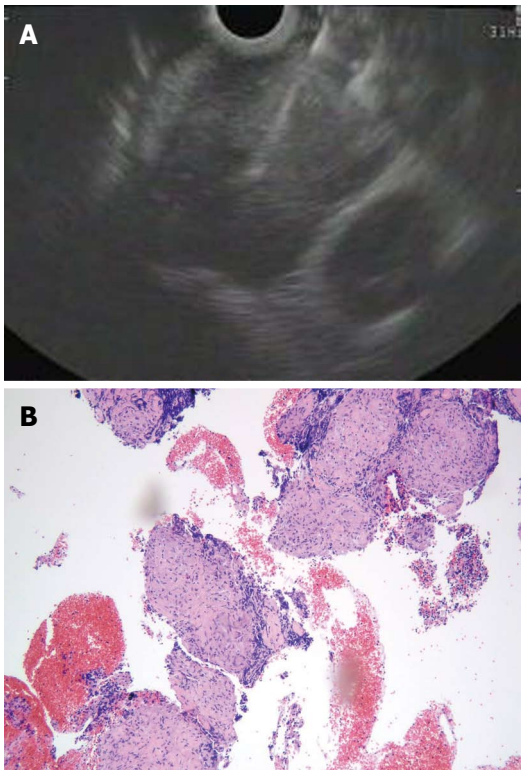

Figure 9 Core biopsy sample can be obtained using the trucut biopsy needle or a standard 19 gauge needle. A: Endoscopic ultrasound-guided fine needle aspiration using a 19 gauge needle of a large subcarinal lymph node in a patient without evidence of any lung mass; B: The histological specimen showed non-necrotizing, non confluent granulomas, diagnostic for sarcoidosis (EE = hematoxylin and eosin x 100).

the need for surgical staging[108], the best results are obtained when the two procedures are used together in a complimentary fashion with a significant reduction in the number of futile thoracotomies than when used alone[109,110]. Moreover, the recent introduction of the endobronchial linear EUS, able to perform transbronchial FNA (EBUS-TBNA) of the anterior mediastinum and to perform, in combination with EUS-FNA, a complete endoscopic mediastinoscopy has revolutionized the approach to the mediastinal staging of NSCLC, which will become more and more an endoscopic than a surgical procedure[111,112].

Mediastinal lesions unrelated to lung or esophageal cancer

Posterior mediastinal lesions representing enlarged lymph nodes or masses can be caused by a variety of benign and malignant diseases other than lung or esophageal cancer. Compared with alternative techniques available for sampling the mediastinum, EUS-FNA is safer and less invasive than CT-guided biopsies or surgical procedures. In cases of suspected lymphoma or sarcoidosis, a core biopsy sample can be more useful than a cytological specimen and can be obtained using the tru cut biopsy needle or a standard 19 gauge needle (Figure 9)[16,23,113]. On the other hand, studies have demonstrated that EUS-FNA with cytological examination has a very high yield to diagnose both lymph node metastases derived from cancers located outside the mediastinum and extra-pulmonary tuberculosis[114,115]. Overall, EUS-FNA has a major impact in the management of 73%-94% of the patients with mediastinal lesions of unknown origin, most frequently by guiding therapy and avoiding surgery[116-118].

Miscellaneous indications

EUS-FNA has been reported to be able to sample lesions of the left and right adrenal glands[112,113,119,120], solid liver lesions[114,121] and more recently, lesions of the left and right kidneys[115,122]. For all these indications, the diagnostic yield of EUS-FNA has been reported to be quite high, with no evidence of procedure related complications apart from one patient with an occluded biliary stent at the time of EUS, who died of cholangitis after EUS-FNA of a liver lesion[114,121].

CONCLUSION

EUS-FNA has become an indispensable tool for the diagnosis and staging of gastrointestinal and thoracic malignancies. In the era of personalized medicine where cancer therapy is more frequently directed by molecular profiling[123], future efforts should be directed towards the development of safe and very accurate methods for acquiring tissue samples that will allow for genetic analysis to identify patients who can benefit from targeted therapies. The potential role of EUS-FNA in molecular diagnostics coupled with the emerging potential of EUS-guided antitumor injection and tumor ablation procedures, will further expand the diagnostic and therapeutic applications of EUS-FNA in the future.

REFERENCES

1 **Henriksen FW**, Hancke S. Percutaneous cystogastrostomy for chronic pancreatic pseudocyst. *Br J Surg* 1994; **81**: 1525-1528
2 **Erickson RA**. EUS-guided FNA. *Gastrointest Endosc* 2004; **60**: 267-279
3 **Voermans RP**, Eisendrath P, Bruno MJ, Le Moine O, Devière J, Fockens P. Initial evaluation of a novel prototype forward-viewing US endoscope in transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2007; **66**: 1013-1017
4 **Binmoeller KF**. Optimizing interventional EUS: the echoendoscope in evolution. *Gastrointest Endosc* 2007; **66**: 917-919
5 **Imazu H**, Uchiyama Y, Kakutani H, Ikeda K, Sumiyama K, Kaise M, Omar S, Ang TL, Tajiri H. A prospective comparison of EUS-guided FNA using 25-gauge and 22-gauge needles. *Gastroenterol Res Pract* 2009; **2009**: 546390
6 **Lee JH**, Stewart J, Ross WA, Anandasabapathy S, Xiao L, Staerkel G. Blinded prospective comparison of the performance of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of the pancreas and peri-pancreatic lesions. *Dig Dis Sci* 2009; **54**: 2274-2281
7 **Siddiqui UD**, Rossi F, Rosenthal LS, Padda MS, Murali-Dharan V, Aslanian HR. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc* 2009; **70**: 1093-1097
8 **Yusuf TE**, Ho S, Pavey DA, Michael H, Gress FG. Retrospec-

tive analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. *Endoscopy* 2009; **41**: 445-448
9 **Levy MJ**, Wiersema MJ. EUS-guided Trucut biopsy. *Gastrointest Endosc* 2005; **62**: 417-426
10 **Levy MJ**, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc* 2003; **57**: 101-106
11 **Larghi A**, Verna EC, Stavropoulos SN, Rotterdam H, Lightdale CJ, Stevens PD. EUS-guided trucut needle biopsies in patients with solid pancreatic masses: a prospective study. *Gastrointest Endosc* 2004; **59**: 185-190
12 **Varadarajulu S**, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, Hoffman BJ, Wallace MB. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy* 2004; **36**: 397-401
13 **Ginès A**, Wiersema MJ, Clain JE, Pochron NL, Rajan E, Levy MJ. Prospective study of a Trucut needle for performing EUS-guided biopsy with EUS-guided FNA rescue. *Gastrointest Endosc* 2005; **62**: 597-601
14 **Wittmann J**, Kocjan G, Sgouros SN, Deheragoda M, Pereira SP. Endoscopic ultrasound-guided tissue sampling by combined fine needle aspiration and trucut needle biopsy: a prospective study. *Cytopathology* 2006; **17**: 27-33
15 **Săftoiu A**, Vilmann P, Guldhammer Skov B, Georgescu CV. Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: a prospective study. *Scand J Gastroenterol* 2007; **42**: 117-125
16 **Storch I**, Shah M, Thurer R, Donna E, Ribeiro A. Endoscopic ultrasound-guided fine-needle aspiration and Trucut biopsy in thoracic lesions: when tissue is the issue. *Surg Endosc* 2008; **22**: 86-90
17 **Thomas T**, Kaye PV, Ragunath K, Aithal G. Efficacy, safety, and predictive factors for a positive yield of EUS-guided Trucut biopsy: a large tertiary referral center experience. *Am J Gastroenterol* 2009; **104**: 584-591
18 **Berger LP**, Scheffer RC, Weusten BL, Seldenrijk CA, de Bruin PC, Timmer R, Stolk MF. The additional value of EUS-guided Tru-cut biopsy to EUS-guided FNA in patients with mediastinal lesions. *Gastrointest Endosc* 2009; **69**: 1045-1051
19 **Ribeiro A**, Vernon S, Quintela P. EUS-guided trucut biopsy with immunohistochemical analysis of a gastric stromal tumor. *Gastrointest Endosc* 2004; **60**: 645-648
20 **Polkowski M**, Gerke W, Jarosz D, Nasierowska-Guttmejer A, Rutkowski P, Nowecki ZI, Ruka W, Regula J, Butruk E. Diagnostic yield and safety of endoscopic ultrasound-guided trucut [corrected] biopsy in patients with gastric submucosal tumors: a prospective study. *Endoscopy* 2009; **41**: 329-334
21 **Fernández-Esparrach G**, Sendino O, Solé M, Pellisé M, Colomo L, Pardo A, Martínez-Pallí G, Argüello L, Bordas JM, Llach J, Ginès A. Endoscopic ultrasound-guided fine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: a randomized crossover study. *Endoscopy* 2010; **42**: 292-299
22 **Iglesias-Garcia J**, Poley JW, Larghi A, Giovannini M, Petrone MC, Abdulkader I, Monges G, Costamagna G, Arcidiacono P, Biermann K, Rindi G, Bories E, Dogloni C, Bruno M, Dominguez-Muñoz JE. Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study. *Gastrointest Endosc* 2011; **73**: 1189-1196
23 **Yasuda I**, Tsurumi H, Omar S, Iwashita T, Kojima Y, Yamada T, Sawada M, Takami T, Moriwaki H, Soehendra N. Endoscopic ultrasound-guided fine-needle aspiration biopsy for lymphadenopathy of unknown origin. *Endoscopy* 2006; **38**: 919-924
24 **Larghi A**, Verna EC, Ricci R, Seerden TC, Galasso D, Carnuccio A, Uchida N, Rindi G, Costamagna G. EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: a prospective study. *Gastrointest Endosc* 2011; **74**: 504-510
25 **Wallace MB**, Kennedy T, Durkalski V, Eloubeidi MA, Etamad R, Matsuda K, Lewin D, Van Velse A, Hennesey W, Hawes RH, Hoffman BJ. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc* 2001; **54**: 441-447
26 **Puri R**, Vilmann P, Săftoiu A, Skov BG, Linnemann D, Hassan H, Garcia ES, Gorunescu F. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol* 2009; **44**: 499-504
27 **Sahai AV**, Paquin SC, Gariépy G. A prospective comparison of endoscopic ultrasound-guided fine needle aspiration results obtained in the same lesion, with and without the needle stylet. *Endoscopy* 2010; **42**: 900-903
28 **Rastogi A**, Wani S, Gupta N, Singh V, Gaddam S, Reddymasu S, Ulusarac O, Fan F, Romanas M, Dennis KL, Sharma P, Bansal A, Oropeza-Vail M, Olyaee M. A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. *Gastrointest Endosc* 2011; **74**: 58-64
29 **Klapman JB**, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol* 2003; **98**: 1289-1294
30 **Alsohaibani F**, Girgis S, Sandha GS. Does onsite cytotechnology evaluation improve the accuracy of endoscopic ultrasound-guided fine-needle aspiration biopsy? *Can J Gastroenterol* 2009; **23**: 26-30
31 **Erickson RA**, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc* 2000; **51**: 184-190
32 **LeBlanc JK**, Ciaccia D, Al-Assi MT, McGrath K, Imperiale T, Tao LC, Vallery S, DeWitt J, Sherman S, Collins E. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc* 2004; **59**: 475-481
33 **Pellisé Urquiza M**, Fernández-Esparrach G, Solé M, Colomo L, Castells A, Llach J, Mata A, Bordas JM, Piqué JM, Ginès A. Endoscopic ultrasound-guided fine needle aspiration: predictive factors of accurate diagnosis and cost-minimization analysis of on-site pathologist. *Gastroenterol Hepatol* 2007; **30**: 319-324
34 **Vazquez-Sequeiros E**, Wiersema MJ, Clain JE, Norton ID, Levy MJ, Romero Y, Salomao D, Dierkhising R, Zinsmeister AR. Impact of lymph node staging on therapy of esophageal carcinoma. *Gastroenterology* 2003; **125**: 1626-1635
35 **Vazquez-Sequeiros E**, Levy MJ, Clain JE, Schwartz DA, Harewood GC, Salomao D, Wiersema MJ. Routine vs. selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma. *Gastrointest Endosc* 2006; **63**: 204-211
36 **Mortensen MB**, Pless T, Durup J, Ainsworth AP, Plagborg GJ, Hovendal C. Clinical impact of endoscopic ultrasound-guided fine needle aspiration biopsy in patients with upper gastrointestinal tract malignancies. A prospective study. *Endoscopy* 2001; **33**: 478-483
37 **Giovannini M**, Monges G, Seitz JF, Moutardier V, Bernardini D, Thomas P, Houvenaeghel G, Delpero JR, Giudicelli R, Fuentes P. Distant lymph node metastases in esophageal cancer: impact of endoscopic ultrasound-guided biopsy. *Endoscopy* 1999; **31**: 536-540
38 **McGrath K**, Brody D, Luketich J, Khalid A. Detection of unsuspected left hepatic lobe metastases during EUS staging of cancer of the esophagus and cardia. *Am J Gastroenterol* 2006; **101**: 1742-1746
39 **Marsman WA**, Brink MA, Bergman JJ, Tytgat GN, ten Kate FJ, van Lanschot JJ, Fockens P. Potential impact of EUS-FNA

staging of proximal lymph nodes in patients with distal esophageal carcinoma. *Endoscopy* 2006; **38**: 825-829
40 **Cerfolio RJ**, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg* 2005; **129**: 1232-1241
41 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20
42 **Mortensen MB**, Fristrup CW, Ainsworth AP, Pless T, Nielsen HO, Hovendal C. Combined preoperative endoscopic and laparoscopic ultrasonography for prediction of R0 resection in upper gastrointestinal tract cancer. *Br J Surg* 2006; **93**: 720-725
43 **Mortensen MB**, Fristrup C, Ainsworth A, Nielsen HO, Pless T, Hovendal C. Combined pretherapeutic endoscopic and laparoscopic ultrasonography may predict survival of patients with upper gastrointestinal tract cancer. *Surg Endosc* 2011; **25**: 804-812
44 **Hassan H**, Vilmann P, Sharma V. Impact of EUS-guided FNA on management of gastric carcinoma. *Gastrointest Endosc* 2010; **71**: 500-504
45 **Harewood GC**, Wiersema MJ, Nelson H, Maccarty RL, Olson JE, Clain JE, Ahlquist DA, Jondal ML. A prospective, blinded assessment of the impact of preoperative staging on the management of rectal cancer. *Gastroenterology* 2002; **123**: 24-32
46 **Shami VM**, Parmar KS, Waxman I. Clinical impact of endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration in the management of rectal carcinoma. *Dis Colon Rectum* 2004; **47**: 59-65
47 **Sasaki Y**, Niwa Y, Hirooka Y, Ohmiya N, Itoh A, Ando N, Miyahara R, Furuta S, Goto H. The use of endoscopic ultrasound-guided fine-needle aspiration for investigation of submucosal and extrinsic masses of the colon and rectum. *Endoscopy* 2005; **37**: 154-160
48 **Hünerbein M**, Totkas S, Moesta KT, Ulmer C, Handke T, Schlag PM. The role of transrectal ultrasound-guided biopsy in the postoperative follow-up of patients with rectal cancer. *Surgery* 2001; **129**: 164-169
49 **Landi B**, Palazzo L. The role of endosonography in submucosal tumours. *Best Pract Res Clin Gastroenterol* 2009; **23**: 679-701
50 **Hoda KM**, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. *Gastrointest Endosc* 2009; **69**: 1218-1223
51 **Mekky MA**, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA, Osman AM, Koshikawa T, Yatabe Y, Bhatia V. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. *Gastrointest Endosc* 2010; **71**: 913-919
52 **Philipper M**, Hollerbach S, Gabbert HE, Heikaus S, Böcking A, Pomjanski N, Neuhaus H, Frieling T, Schumacher B. Prospective comparison of endoscopic ultrasound-guided fine-needle aspiration and surgical histology in upper gastrointestinal submucosal tumors. *Endoscopy* 2010; **42**: 300-305
53 **Casali PG**, Blay JY. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** Suppl 5: v98-102
54 **Eloubeidi MA**, Tamhane A, Varadarajulu S, Wilcox CM. Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation. *Gastrointest Endosc* 2006; **63**: 622-629
55 **Chang KJ**. State of the art lecture: endoscopic ultrasound (EUS) and FNA in pancreatico-biliary tumors. *Endoscopy* 2006; **38** Suppl 1: S56-S60
56 **Boujaoude J**. Role of endoscopic ultrasound in diagnosis and therapy of pancreatic adenocarcinoma. *World J Gastroenterol* 2007; **13**: 3662-3666
57 **Horwhat JD**, Paulson EK, McGrath K, Branch MS, Baillie J, Tyler D, Pappas T, Enns R, Robuck G, Stiffler H, Jowell P. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions. *Gastrointest Endosc* 2006; **63**: 966-975
58 **Eisen GM**, Dominitz JA, Faigel DO, Goldstein JA, Petersen BT, Raddawi HM, Ryan ME, Vargo JJ, Young HS, Wheeler-Harbaugh J, Hawes RH, Brugge WR, Carrougher JG, Chak A, Faigel DO, Kochman ML, Savides TJ, Wallace MB, Wiersema MJ, Erickson RA. Guidelines for credentialing and granting privileges for endoscopic ultrasound. *Gastrointest Endosc* 2001; **54**: 811-814
59 **DeWitt J**, LeBlanc J, McHenry L, Ciaccia D, Imperiale T, Chappo J, Cramer H, McGreevy K, Chriswell M, Sherman S. Endoscopic ultrasound-guided fine needle aspiration cytology of solid liver lesions: a large single-center experience. *Am J Gastroenterol* 2003; **98**: 1976-1981
60 **DeWitt J**, LeBlanc J, McHenry L, McGreevy K, Sherman S. Endoscopic ultrasound-guided fine-needle aspiration of ascites. *Clin Gastroenterol Hepatol* 2007; **5**: 609-615
61 **DeWitt J**, Yu M, Al-Haddad MA, Sherman S, McHenry L, Leblanc JK. Survival in patients with pancreatic cancer after the diagnosis of malignant ascites or liver metastases by EUS-FNA. *Gastrointest Endosc* 2010; **71**: 260-265
62 **Micames C**, Jowell PS, White R, Paulson E, Nelson R, Morse M, Hurwitz H, Pappas T, Tyler D, McGrath K. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. *Gastrointest Endosc* 2003; **58**: 690-695
63 **Eloubeidi MA**, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. *J Gastroenterol Hepatol* 2008; **23**: 567-570
64 **Tadic M**, Kujundzic M, Stoos-Veic T, Kaic G, Vukelic-Markovic M. Role of repeated endoscopic ultrasound-guided fine needle aspiration in small solid pancreatic masses with previous indeterminate and negative cytological findings. *Dig Dis* 2008; **26**: 377-382
65 **Hartwig W**, Schneider L, Diener MK, Bergmann F, Büchler MW, Werner J. Preoperative tissue diagnosis for tumours of the pancreas. *Br J Surg* 2009; **96**: 5-20
66 **Mortenson MM**, Katz MH, Tamm EP, Bhutani MS, Wang H, Evans DB, Fleming JB. Current diagnosis and management of unusual pancreatic tumors. *Am J Surg* 2008; **196**: 100-113
67 **Napoleon B**, Alvarez-Sanchez MV, Gincoul R, Pujol B, Lefort C, Lepilliez V, Labadie M, Souquet JC, Queneau PE, Scoazec JY, Chayvialle JA, Ponchon T. Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. *Endoscopy* 2010; **42**: 564-570
68 **Iglesias-Garcia J**, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010; **139**: 1172-1180
69 **Khalid A**, Nodit L, Zahid M, Bauer K, Brody D, Finkelstein SD, McGrath KM. Endoscopic ultrasound fine needle aspirate DNA analysis to differentiate malignant and benign pancreatic masses. *Am J Gastroenterol* 2006; **101**: 2493-2500
70 **Bournet B**, Souque A, Senesse P, Assenat E, Barthet M, Lesavre N, Aubert A, O'Toole D, Hammel P, Levy P, Ruszniewski P, Bouisson M, Escourrou J, Cordelier P, Buscail L. Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with KRAS mutation assay to distinguish pancreatic cancer from pseudotumoral chronic pancreatitis. *Endoscopy* 2009; **41**: 552-557
71 **Maluf-Filho F**, Kumar A, Gerhardt R, Kubrusly M, Sakai P, Hondo F, Matuguma SE, Artifon E, Monteiro da Cunha

JE, César Machado MC, Ishioka S, Forero E. Kras mutation analysis of fine needle aspirate under EUS guidance facilitates risk stratification of patients with pancreatic mass. *J Clin Gastroenterol* 2007; **41**: 906-910
72 **Mizuno N**, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, Takagi T, Ko SB, Yatabe Y, Goto H, Yamao K. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. *J Gastroenterol* 2009; **44**: 742-750
73 **Al-Haddad M**, Savabi MS, Sherman S, McHenry L, Leblanc J, Cramer H, Emerson R, O'Neil J, Khashab M, Dewitt J. Role of endoscopic ultrasound-guided fine-needle aspiration with flow cytometry to diagnose lymphoma: a single center experience. *J Gastroenterol Hepatol* 2009; **24**: 1826-1833
74 **Figueiredo FA**, Giovannini M, Monges G, Charfi S, Bories E, Pesenti C, Caillol F, Delpero JR. Pancreatic endocrine tumors: a large single-center experience. *Pancreas* 2009; **38**: 936-940
75 **Pais SA**, Al-Haddad M, Mohamadnejad M, Leblanc JK, Sherman S, McHenry L, DeWitt JM. EUS for pancreatic neuroendocrine tumors: a single-center, 11-year experience. *Gastrointest Endosc* 2010; **71**: 1185-1193
76 **Figueiredo FA**, Giovannini M, Monges G, Bories E, Pesenti C, Caillol F, Delpero JR. EUS-FNA predicts 5-year survival in pancreatic endocrine tumors. *Gastrointest Endosc* 2009; **70**: 907-914
77 **Piani C**, Franchi GM, Cappelletti C, Scavini M, Albarello L, Zerbi A, Giorgio Arcidiacono P, Bosi E, Manzoni MF. Cytological Ki-67 in pancreatic endocrine tumours: an opportunity for pre-operative grading. *Endocr Relat Cancer* 2008; **15**: 175-181
78 **Klöppel G**, Couvelard A, Perren A, Komminoth P, McNicol AM, Nilsson O, Scarpa A, Scoazec JY, Wiedenmann B, Papotti M, Rindi G, Plöckinger U. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology* 2009; **90**: 162-166
79 **Spier BJ**, Johnson EA, Gopal DV, Frick T, Einstein MM, Byrne S, Koscik RL, Liou JI, Broxmeyer T, Selvaggi SM, Pfau PR. Predictors of malignancy and recommended follow-up in patients with negative endoscopic ultrasound-guided fine-needle aspiration of suspected pancreatic lesions. *Can J Gastroenterol* 2009; **23**: 279-286
80 **Brugge WR**, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. *N Engl J Med* 2004; **351**: 1218-1226
81 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336
82 **van der Waaij LA**, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest Endosc* 2005; **62**: 383-389
83 **Linder JD**, Geenen JE, Catalano MF. Cyst fluid analysis obtained by EUS-guided FNA in the evaluation of discrete cystic neoplasms of the pancreas: a prospective single-center experience. *Gastrointest Endosc* 2006; **64**: 697-702
84 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102
85 **Sawhney MS**, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, Brown A, Chuttani R, Pleskow DK. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; **69**: 1106-1110
86 **Cuoghi A**, Farina A, Z'graggen K, Dumonceau JM, Tomasi A, Hochstrasser DF, Genevay M, Lescuyer P, Frossard JL. Role of proteomics to differentiate between benign and potentially malignant pancreatic cysts. *J Proteome Res* 2011; **10**: 2664-2670
87 **Levy MJ**, Smyrk TC, Reddy RP, Clain JE, Harewood GC, Kendrick ML, Pearson RK, Petersen BT, Rajan E, Topazian MD, Wang KK, Wiersema MJ, Yusuf TE, Chari ST. Endoscopic ultrasound-guided trucut biopsy of the cyst wall for diagnosing cystic pancreatic tumors. *Clin Gastroenterol Hepatol* 2005; **3**: 974-979
88 **Al-Haddad M**, Gill KR, Raimondo M, Woodward TA, Krishna M, Crook JE, Skarvinko LN, Jamil LH, Hasan M, Wallace MB. Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study. *Endoscopy* 2010; **42**: 127-132
89 **Sendino O**, Fernández-Esparrach G, Solé M, Colomo L, Pellisé M, Llach J, Navarro S, Bordas JM, Ginès A. Endoscopic ultrasonography-guided brushing increases cellular diagnosis of pancreatic cysts: A prospective study. *Dig Liver Dis* 2010; **42**: 877-881
90 **Fritscher-Ravens A**, Broering DC, Sriram PV, Topalidis T, Jaeckle S, Thonke F, Soehendra N. EUS-guided fine-needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest Endosc* 2000; **52**: 534-540
91 **DeWitt J**, Misra VL, Leblanc JK, McHenry L, Sherman S. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. *Gastrointest Endosc* 2006; **64**: 325-333
92 **Pavey DA**, Gress FG. The role of EUS-guided FNA for the evaluation of biliary strictures. *Gastrointest Endosc* 2006; **64**: 334-337
93 **Larghi A**, Lecca PG, Ardito F, Rossi ED, Fadda G, Nuzzo G, Costamagna G. Evaluation of hilar biliary strictures by using a newly developed forward-viewing therapeutic echoendoscope: preliminary results of an ongoing experience. *Gastrointest Endosc* 2009; **69**: 356-360
94 **Rea DJ**, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; **242**: 451-48; discussion 451-48;
95 **Gleeson FC**, Rajan E, Levy MJ, Clain JE, Topazian MD, Harewood GC, Papachristou GI, Takahashi N, Rosen CB, Gores GJ. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. *Gastrointest Endosc* 2008; **67**: 438-443
96 **Vilmann P**, Annema J, Clementsen P. Endosonography in bronchopulmonary disease. *Best Pract Res Clin Gastroenterol* 2009; **23**: 711-728
97 **Herbst RS**, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med* 2008; **359**: 1367-1380
98 **Annema JT**, Veseliç M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. *Lung Cancer* 2005; **48**: 357-61; discussion 363-4
99 **Singh P**, Camazine B, Jadhav Y, Gupta R, Mukhopadhyay P, Khan A, Reddy R, Zheng Q, Smith DD, Khode R, Bhatt B, Bhat S, Yaqub Y, Shah RS, Sharma A, Sikka P, Erickson RA. Endoscopic ultrasound as a first test for diagnosis and staging of lung cancer: a prospective study. *Am J Respir Crit Care Med* 2007; **175**: 345-354
100 **Larsen SS**, Vilmann P, Krasnik M, Dirksen A, Clementsen P, Maltbaek N, Lassen U, Skov BG, Jacobsen GK. Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial. *Lung Cancer* 2005; **49**: 377-385
101 **Annema JT**, Versteegh MI, Veseliç M, Voigt P, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of lung cancer and its impact on surgical staging. *J Clin Oncol* 2005; **23**: 8357-8361
102 **Wallace MB**, Ravenel J, Block MI, Fraig M, Silvestri G, Wildi S, Schmulewitz N, Varadarajulu S, Roberts S, Hoffman BJ,

Hawes RH, Reed CE. Endoscopic ultrasound in lung cancer patients with a normal mediastinum on computed tomography. *Ann Thorac Surg* 2004; **77**: 1763-1768
103 **Annema JT**, Hoekstra OS, Smit EF, Veseliç M, Versteegh MI, Rabe KF. Towards a minimally invasive staging strategy in NSCLC: analysis of PET positive mediastinal lesions by EUS-FNA. *Lung Cancer* 2004; **44**: 53-60
104 **Eloubeidi MA**, Cerfolio RJ, Chen VK, Desmond R, Syed S, Ojha B. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg* 2005; **79**: 263-268
105 **Kalade AV**, Eddie Lau WF, Conron M, Wright GM, Desmond PV, Hicks RJ, Chen R. Endoscopic ultrasound-guided fine-needle aspiration when combined with positron emission tomography improves specificity and overall diagnostic accuracy in unexplained mediastinal lymphadenopathy and staging of non-small-cell lung cancer. *Intern Med J* 2008; **38**: 837-844
106 **Fischer BM**, Mortensen J, Hansen H, Vilmann P, Larsen SS, Loft A, Bertelsen AK, Ravn J, Clementsen P, Høegholm A, Larsen KR, Dirksen A, Skov BG, Krasnik M, Højgaard L, Lassen U. Multimodality approach to mediastinal staging in non-small cell lung cancer. Faults and benefits of PET-CT: a randomised trial. *Thorax* 2011; **66**: 294-300
107 **Schuurbiers OC**, Tournoy KG, Schoppers HJ, Dijkman BG, Timmers HJ, de Geus-Oei LF, Grefte JM, Rabe KF, Dekhuijzen PN, van der Heijden HF, Annema JT. EUS-FNA for the detection of left adrenal metastasis in patients with lung cancer. *Lung Cancer* 2011; **73**: 310-315
108 **Tournoy KG**, De Ryck F, Vanwalleghem LR, Vermassen F, Praet M, Aerts JG, Van Maele G, van Meerbeeck JP. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. *Am J Respir Crit Care Med* 2008; **177**: 531-535
109 **Annema JT**, Versteegh MI, Veseliç M, Welker L, Mauad T, Sont JK, Willems LN, Rabe KF. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. *JAMA* 2005; **294**: 931-936
110 **Witte B**, Neumeister W, Huertgen M. Does endoesophageal ultrasound-guided fine-needle aspiration replace mediastinoscopy in mediastinal staging of thoracic malignancies? *Eur J Cardiothorac Surg* 2008; **33**: 1124-1128
111 **Annema JT**, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, De Leyn P, Braun J, Carroll NR, Praet M, de Ryck F, Vansteenkiste J, Vermassen F, Versteegh MI, Veseliç M, Nicholson AG, Rabe KF, Tournoy KG. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010; **304**: 2245-2252
112 **Wallace MB**, Pascual JM, Raimondo M, Woodward TA, McComb BL, Crook JE, Johnson MM, Al-Haddad MA, Gross SA, Pungpapong S, Hardee JN, Odell JA. Minimally invasive endoscopic staging of suspected lung cancer. *JAMA* 2008; **299**: 540-546
113 **Iwashita T**, Yasuda I, Doi S, Kato T, Sano K, Yasuda S, Nakashima M, Hirose Y, Takaimi T, Moriwaki H. The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. *Endoscopy* 2008; **40**: 400-405
114 **Peric R**, Schuurbiers OC, Veseliç M, Rabe KF, van der Heijden HF, Annema JT. Transesophageal endoscopic ultrasound-guided fine-needle aspiration for the mediastinal staging of extrathoracic tumors: a new perspective. *Ann Oncol* 2010; **21**: 1468-1471
115 **Puri R**, Vilmann P, Sud R, Kumar M, Taneja S, Verma K, Kaushik N. Endoscopic ultrasound-guided fine-needle aspiration cytology in the evaluation of suspected tuberculosis in patients with isolated mediastinal lymphadenopathy. *Endoscopy* 2010; **42**: 462-467
116 **Catalano MF**, Rosenblatt ML, Chak A, Sivak MV, Scheiman J, Gress F. Endoscopic ultrasound-guided fine needle aspiration in the diagnosis of mediastinal masses of unknown origin. *Am J Gastroenterol* 2002; **97**: 2559-2565
117 **Larsen SS**, Krasnik M, Vilmann P, Jacobsen GK, Pedersen JH, Faurschou P, Folke K. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. *Thorax* 2002; **57**: 98-103
118 **Savides TJ**, Perricone A. Impact of EUS-guided FNA of enlarged mediastinal lymph nodes on subsequent thoracic surgery rates. *Gastrointest Endosc* 2004; **60**: 340-346
119 **Eloubeidi MA**, Black KR, Tamhane A, Eltoum IA, Bryant A, Cerfolio RJ. A large single-center experience of EUS-guided FNA of the left and right adrenal glands: diagnostic utility and impact on patient management. *Gastrointest Endosc* 2010; **71**: 745-753
120 **DeWitt J**, Alsatie M, LeBlanc J, McHenry L, Sherman S. Endoscopic ultrasound-guided fine-needle aspiration of left adrenal gland masses. *Endoscopy* 2007; **39**: 65-71
121 **tenBerge J**, Hoffman BJ, Hawes RH, Van Enckevort C, Giovannini M, Erickson RA, Catalano MF, Fogel R, Mallery S, Faigel DO, Ferrari AP, Waxman I, Palazzo L, Ben-Menachem T, Jowell PS, McGrath KM, Kowalski TE, Nguyen CC, Wassef WY, Yamao K, Chak A, Greenwald BD, Woodward TA, Vilmann P, Sabbagh L, Wallace MB. EUS-guided fine needle aspiration of the liver: indications, yield, and safety based on an international survey of 167 cases. *Gastrointest Endosc* 2002; **55**: 859-862
122 **DeWitt J**, Gress FG, Levy MJ, Hernandez LV, Eloubeidi MA, Mishra G, Sherman S, Al-Haddad MA, LeBlanc JK. EUS-guided FNA aspiration of kidney masses: a multicenter U.S. experience. *Gastrointest Endosc* 2009; **70**: 573-578
123 **Hamburg MA**, Collins FS. The path to personalized medicine. *N Engl J Med* 2010; **363**: 301-304

S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.545

World J Gastrointest Endosc 2012 December 16; 4(12): 545-555
ISSN 1948-5190 (online)

MINIREVIEWS

Image-enhanced endoscopy for diagnosis of colorectal tumors in view of endoscopic treatment

Naohisa Yoshida, Nobuaki Yagi, Akio Yanagisawa, Yuji Naito

Naohisa Yoshida, Nobuaki Yagi, Yuji Naito, Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan
Akio Yanagisawa, Department of Surgical Pathology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto 602-8566, Japan
Author contributions: All of the authors contributed equally to this work.
Correspondence to: Naohisa Yoshida, MD, PhD, Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. naohisa@koto.kpu-m.ac.jp
Telephone: +81-75-2515519 Fax: +81-75-2510710
Received: December 8, 2011 Revised: October 29, 2012
Accepted: November 25, 2012
Published online: December 16, 2012

Abstract

Recently, image-enhanced endoscopy (IEE) has been used to diagnose gastrointestinal tumors. This method is a change from conventional white-light (WL) endoscopy without dyeing solution, requiring only the push of a button. In IEE, there are many advantages in diagnosis of neoplastic tumors, evaluation of invasion depth for cancerous lesions, and detection of neoplastic lesions. In narrow band imaging (NBI) systems (Olympus Medical Co., Tokyo, Japan), optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are used. Mucosal surface blood vessels are seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while vessels in the deep layer of the mucosa can be detected at 540 nm. Thus, NBI also can detect pit-like structures named surface pattern. The flexible spectral imaging color enhancement (FICE) system (Fujifilm Medical Co., Tokyo, Japan) is also an IEE but different to NBI. FICE depends on the use of spectral-estimation technology to reconstruct images at different wavelengths based on WL images. FICE can enhance vascular and surface patterns. The autofluorescence imaging (AFI) video endoscope system (Olympus Medical Co., Tokyo, Japan) is a new illumination method that uses the difference in intensity of autofluorescence between the normal area and neoplastic lesions. AFI light comprises a blue light for emitting and a green light for hemoglobin absorption. The aim of this review is to highlight the efficacy of IEE for diagnosis of colorectal tumors for endoscopic treatment.

Key words: Flexible spectral imaging color enhancement; Narrow band imaging; Autofluorescence imaging; Colorectal polyps; Image-enhanced endoscopy

Peer reviewer: Vittorio Terruzzi, MD, Department of Gastroenterology, Ospedale Valduce, Via Dante, 11 22100 Como, Italy

Yoshida N, Yagi N, Yanagisawa A, Naito Y. Image-enhanced endoscopy for diagnosis of colorectal tumors in view of endoscopic treatment. *World J Gastrointest Endosc* 2012; 4(12): 545-555 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/545.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.545

INTRODUCTION

Colorectal cancer is a common gastrointestinal malignancy in United States, Europe and Japan. Most colorectal cancers are thought to arise from preexisting adenomas based on the concept of the adenoma-carcinoma sequence[1]. Therefore, adenomatous polyps should be resected using endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)[2-4]. Colonoscopy is considered an effective examination for the detection of colorectal neoplastic lesions. However, the diagnostic capability of white-light (WL) endoscopy for the differentiation of neoplastic and

non-neoplastic polyps has demonstrated low sensitivity (38%-76%) and variable specificity (66%-97%)[5-7]. On the other hand, chromoendoscopy, using Kudo and Tsuruta's pit pattern classification, is a powerful tool for differential diagnosis of colorectal polyps[7-9]. The diagnostic capability of chromoendoscopy for the differentiation of neoplastic and non-neoplastic polyps has demonstrated high sensitivity (96.3%-97.0%) and high specificity (93.5%-100%)[10,11]. However, the operation of chromoendoscopy is relatively cumbersome, time-consuming and costly, not conducive to observe the vascular structure. Recently, image-enhanced endoscopy (IEE) has been carried out to diagnose gastrointestinal tumors. This method is a change from conventional WL without the need for a dyeing solution, requiring only the push of a button. In IEE, including narrow-band imaging (NBI), flexible spectral imaging color enhancement (FICE) and autofluorescence imaging (AFI), there are many advantages in diagnosis of neoplastic tumors, evaluation of invasion depth for cancerous lesions, and detection of neoplastic lesions. The aim of this review is to support the efficacy of IEE for diagnosis of colorectal tumors with a view to endoscopic treatment.

PRINCIPLE OF IEE: NBI, FICE AND AFI

In the NBI systems (Olympus Medical Co., Tokyo, Japan), optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon arc lamp and a red/green/blue rotatable filter[12-16]. Narrow mucosal surface blood vessels are seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while thick vessels in the deep layer of the mucosa can be detected at 540 nm. Thus, NBI with or without magnification, can enhance vascular patterns. Moreover, NBI also can detect the pit-like structures, which were named surface patterns in the Japanese consensus symposium[17]. On the other hand, the FICE system (Fujifilm Medical Co., Tokyo, Japan) is also an IEE but is unlike NBI. Previously, FICE was defined as "Fuji Intelligent Color Endoscopy", but this definition has been changed recently. FICE depends on the use of spectral-estimation technology to reconstruct images at different wavelengths based on WL images[18]. The suitable RGB wavelength settings and each wavelength contrast level for FICE to evaluate colorectal polyp were 540 (1), 460 (4), and 460 (4) nm, respectively[19]. FICE with or without magnification can enhance vascular and surface patterns[6,7,19-22]. The AFI system (Olympus Medical Co., Tokyo, Japan) is a new illumination method that uses the difference in intensity of autofluorescence between normal areas and neoplastic lesions[23-25]. AFI light comprises a blue light for emitting and a green light for hemoglobin absorption. Neoplastic areas involve a thickening of the mucosal layer and increased hemoglobin so such areas emit weaker autofluorescence compared to non-neoplastic areas. Recently, the AFI system has been used to enhance detection of early lesions in the esophagus, stomach, and colon.

IEE WITHOUT MAGNIFICATION

Magnifying endoscopy is less common in United States, and Europe. Therefore, accurate diagnosis of colorectal polyps using endoscopy without magnification is required. In NBI, high-definition colonoscopy, without magnification, is reported to be able to predict whether a colorectal polyp is neoplastic or non-neoplastic[26,27]. Various studies about NBI without magnification demonstrated accuracy of 89.0%-92.7%, sensitivity of 87.9%-95.7% and specificity of 87.0%-90.5% (Table 1)[26-29]. On the other hand, FICE without magnification is also reported to be useful for differentiation between a neoplastic polyp and non-neoplastic polyp. Various studies about FICE without magnification, demonstrated accuracy of 84.4%-89.4%, sensitivity of 89.4%-93.2% and specificity of 81.2%-88.0% almost similar to the data of the NBI studies (Table 1)[7,19,30].

A meshed capillary network is one of the important endoscopic features of neoplastic polyps in NBI without magnification, as defined by Sano *et al*[14](Figure 1). Other reports using NBI without magnification also point to meshed capillary vessels as being characteristic of neoplastic polyps[27]. Rex[28] adopted surface patterns including pit and vascular patterns for neoplastic endoscopic features in NBI. Rastogi *et al*[5] used 5 different surface patterns (including mucosal, pit and vascular patterns) to differentiate neoplastic polyps from non-neoplastic polyps. In FICE, the detection of surface patterns is a reliable method to determine whether a polyp is neoplastic or non-neoplastic though one study demonstrated evaluation of vascular patterns (Figure 2). The reason was that FICE without magnification could not detect detail vascular patterns clearly compared to NBI[19].

In a report about NBI without magnification, when polyp size was considered, the accuracy in polyps 6-9 mm in diameter (accuracy: 96.0%) were better than those for polyps 5 mm or less in diameter (accuracy: 90.0%)[27]. In FICE without magnification, the accuracy, sensitivity, and specificity in polyps 6 mm or greater in diameter (97.1%, 95.2%, 90.0%) were better than for polyps 5 mm or less in diameter (82.7%, 78.0%, 87.5%)[19,31]. Diagnosis of small polyps is important for the prevention of colorectal cancer. A procedural decision to avoid resection of non-neoplastic polyps would spare patients the cost and risk of a polypectomy. The DISCARD trial reported by Ignjatovic *et al*[32] demonstrates that for polyps less than 10 mm in size, *in-vivo* optical diagnosis including NBI without magnification seems to be an acceptable strategy to differentiate adenomatous polyp from hyperplastic polyp (sensitivity: 94%, specificity 89%).

Recently, an international cooperative group was formed and consists of members from Japan, United States and Europe, named the Colon Tumor NBI Interest Group. This group has developed NBI international

Table 1 Reports about image-enhanced endoscopy without magnification for differentiation between neoplastic polyps and non-neoplastic polyps (%)

Ref.	System	No. of cases	Accuracy	Sensitivity	Specificity	PPV	NPV
Henry *et al*[27]	NBI	126	90.0	93.0	88.0	93.0	91.0
Su *et al*[29]	NBI	110	92.7	95.7	87.5	93.0	92.1
Tischendorf *et al*[26]	NBI	100	89.0	87.9	90.5	92.7	84.4
Rex[28]	NBI	451	89.0	92.0	87.0	88.0	91.0
Lonqcroft-Wheaton GR	FICE	232	88.0	-	-	-	-
Pohl *et al*[61]	FICE	321	84.4	93.2	61.2	88.0	76.4
Yoshida *et al*[22]	FICE	151	89.4	89.4	88.0	93.4	83.3
Sato *et al*[34]	AFI	358	91.9	92.7	92.9	-	-

NBI: Narrow-band imaging; FICE: Flexible spectral imaging color enhancement; PPV: Positive predictive value; NPV: Negative predictive value; AFI: Autofluorescence imaging.

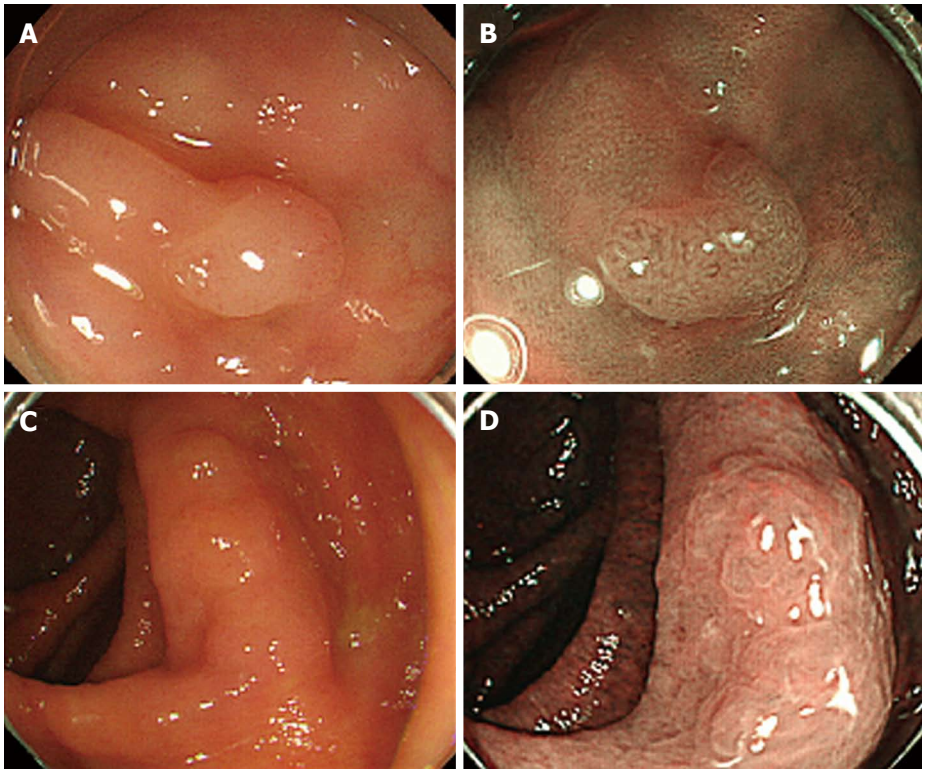

Figure 1 Narrow band imaging without magnification. A: Ⅰa polyp 3 mm in diameter. White-light (WI) endoscopy figure; B: Meshed capillary pattern and oval surface pattern were detected with narrow band imaging (NBI) without magnification. The polyp was diagnosed as a neoplastic polyp; C: Ⅱa polyp 16 mm in diameter. WI endoscopy figure; D: Meshed capillary pattern was not detected with NBI without magnification, but a round surface pattern was detected. The polyp was diagnosed as a non-neoplastic polyp.

colorectal endoscopic (NICE) classification, which classifies colorectal tumors into types 1-3 by closely observing colorectal tumors without magnification[17]. Now, NICE classification of the capability of differential diagnosis between non-neoplastic polyp, adenoma, and cancer in United States, Europe and Japan has been validated.

AFI has been reported to have an advantage in providing better visualization of polyps than WL and, therefore, may be able to improve the capability of differential diagnosis between neoplastic and non-neoplastic polyps and the detection of adenomas[33]. Some reports demonstrated that AFI may be more effective for the characterization of colorectal adenomas because of better visualization of such lesions compared to NBI (Table1, Figure 3)[33,34].

NBI AND FICE WITH MAGNIFICATION FOR THE DIFFERENTIATION OF NEOPLASTIC OR NON-NEOPLASTIC AND DIAGNOSIS OF CANCER DEPTH

There have been many studies on NBI and FICE with magnification[12-14,35-37]. In the differentiation of neoplastic or non-neoplastic polyps, these studies reported an accuracy of 93.4%-98.9%, sensitivity of 90.9%-100.0%, specificity of 75.0%-98.9%, positive predictive value

Table 2 Reports about image-enhanced endoscopy with magnification for differentiation between neoplastic polyps and non-neoplastic polyps (%)

Ref.	System	No. of cases	Accuracy	Sensitivity	Specificity	PPV	NPV
Machida *et al*[12]	NBI	43	93.4	100.0	75.0	91.2	100.0
Sano *et al*[14]	NBI	150	95.3	96.4	92.3	97.3	90.0
Wada *et al*[35]	NBI	617	96.7	90.9	97.1	-	-
Tanaka *et al*[17]	NBI	289	98.9	100.0	98.9	-	-
Togashi *et al*[6]	FICE	107	87.0	93.0	70.0	90.0	76.0
dos Santos *et al*[20]	FICE	111	92.8	97.8	79.3	93.0	92.0

NBI: Narrow-band imaging; FICE: Flexible spectral imaging color enhancement; PPV: Positive predictive value; NPV: Negative predictive value.

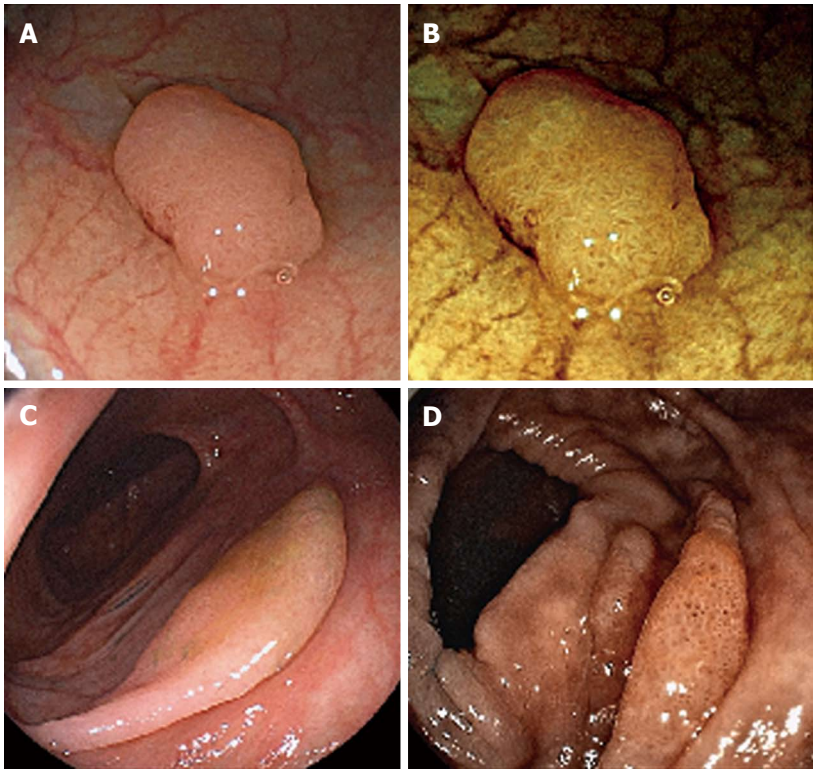

Figure 2 Flexible spectral imaging color enhancement without magnification. A: Ⅰa polyp 5 mm in diameter. White-light (WI) endoscopy figure; B: Flexible spectral imaging color enhancement (FICE) without magnification. FICE settings were RGB wavelengths 550, 500 and 470 nm. Round pits were identified as non-neoplastic surface patterns; C: Ⅱa polyp 16 mm in diameter. WI endoscopy figure; D: Meshed capillary pattern was not detected with FICE without magnification, but round surface pattern was detected. The polyp was diagnosed as a non-neoplastic polyp.

(PPV) of 91.2%-97.3%, and negative predictive value (NPV) of 90.0%-100.0% (Table 2). There are four published classifications of NBI with magnification such as the Sano classification, Hiroshima classification, Showa classification, Jikei classification and one published FICE classification[14,16,21,35,38]. In brief, the Sano classification, Showa classification and Jikei classification classify using only vascular pattern. On the other hand, the Hiroshima classification and FICE classification use surface and vascular patterns. The efficacy of surface pattern detection in NBI and FICE magnification has been reported previously[16,21]. We have reported on the detectability of NBI and FICE with magnification and the difference between them[21]. In that, in magnifying endoscopy NBI could detect thinner vessels than FICE could (Figure 4). The avascular area detected in deeply submucosal invasive cancer by NBI is observed frequently in FICE. So, massively submucosal invasive cancer cannot be diagnosed only by the avascular area in FICE[21]. Thus, observation with FICE requires both vascular pattern and surface pattern and thus FICE classification was defined, modifying the Hiroshima classification of NBI[21].

The accuracy, sensitivity, and specificity of each NBI and FICE classification for massively submucosal invasive cancer are described in Table 3[14,16,21,35,39]. These studies reported accuracy of 87.7%-98.3%, sensitivity of 77.7%-100.0%, specificity of 88.7%-100.0%, PPV of 71.8%-100.0%, and NPV of 90.0%-96.2%. Therefore, NBI and FICE magnification were thought to be useful for determining therapeutic strategies, including

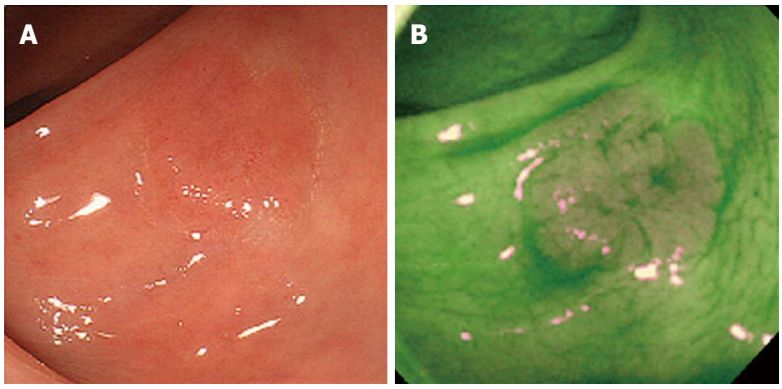

Figure 3 Autofluorescence imaging. A: Ⅱa polyp 14 mm in diameter (White-light endoscopy figure); B: In autofluorescence imaging, the normal mucosa was detected by green color and the neoplastic polyp was detected by magenta color.

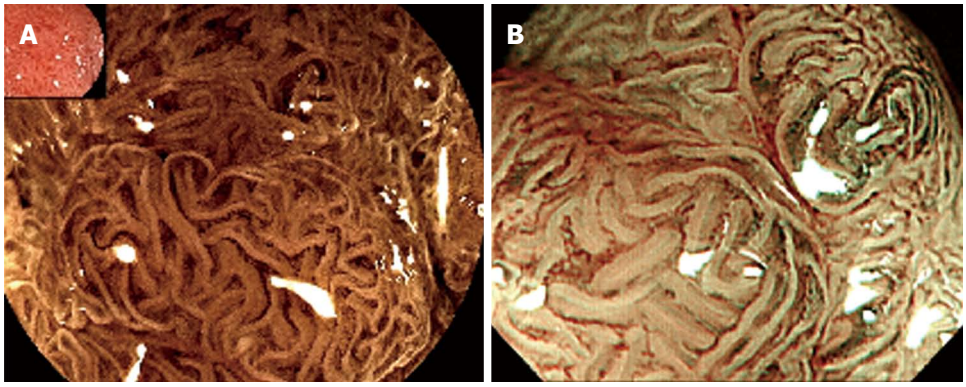

Figure 4 The surface and vascular patterns as seen by flexible spectral imaging color enhancement magnification and narrow band imaging magnification are shown. A: Flexible spectral imaging color enhancement; B: Narrow band imaging.

endoscopic resection by EMR, ESD, or surgical operation of colorectal tumors. However, the sensitivity (77.7%-100.0%) and the specificity (88.7%-100.0%) were not sufficient. Chromoendoscopy using pit pattern classification should be performed in a case which is suspected as cancerous with NBI and FICE or which is diagnosed by NBI and FICE with low confidence.

Recent studies have reported outcomes of training in NBI with magnification for the differentiation of neoplastic or non-neoplastic polyps. These studies revealed that a 20-60 min training lecture could increase the differential diagnostic skills of operators inexperienced in NBI with magnification to expert levels[40,41].

Sano classification

Based on the surface characteristics of the meshed capillaries (Figure 5)[14], capillary pattern (CP) type I is defined as invisible meshed capillary pattern, detected in hyperplastic polyps (Figure 5A). CP type Ⅱ is the regular small-caliber capillaries observed in adenomatous polyps (Figure 5B). CP type Ⅲ is defined as demonstrating irregular and unarranged patterns in a mesh-like microvascular architecture, exhibiting at least one of the following: irregular size, complicated branching, disrupted irregular winding. Moreover, CP type Ⅲ lesions are further classified into two groups: types ⅢA or ⅢB according to microvascular architecture and high microvessel density with lack of uniformity, blind ending, branching and curtailed irregularly (Figure 5 C-E). CP type ⅢA is observed mainly in adenoma, intramucosal cancer and slightly invaded submucosal cancer. CP type ⅢB is observed 28% in intramucosal cancer and 72% in massively invaded submucosal cancer (Figure 6).

Hiroshima classification

Hiroshima classification classifies according to vascular pattern and surface pattern such as type A, type B, or type C[16]. NBI magnification findings are considered: type A when microvessels are not observed or are extremely opaque; type B when fine microvessels are observed around the surface patterns and clear surface patterns can be observed *via* the nest of microvessels; and type C when the microvessels are irregular and the vessel diameter or distribution is heterogeneous (Figure 5). Type A is observed in hyperplastic polyps and type B is observed mainly in adenoma and intramucosal cancer. Type C is divided into 3 subtypes (C1, C2 and C3) according to: surface patterns visibility, vessel diameter, irregularity, and distribution. In type C1, microvessels comprise an irregular network, surface patterns observed *via* the microvessels are slightly non distinct and vessel diameter or distribution is homogeneous (Figure 5C). In the previous

Table 3 Reports about image-enhanced endoscopy with magnification for differentiation of massively submocosal invasive cancer (%)

Ref.	System	No. of cases	Accuracy	Sensitivity	Specificity	PPV	NPV
Fukuzawa *et al*[39]	NBI	112	92.9	81.4	100.0	100.0	90.0
Wada *et al*[35]	NBI	584	96.1	100.0	95.8	-	-
Tanaka *et al*[17]	NBI	97	94.1	63.8	100.0	-	-
Ikematsu *et al*[58]	NBI	130	87.7	84.8	88.7	71.8	94.5
Yoshida *et al*[22]	FICE	124	98.3	77.7	100.0	100.0	98.2

NBI: Narrow-band imaging; FICE: Flexible spectral imaging color enhancement; PPV: Positive predictive value; NPV: Negative predictive value.

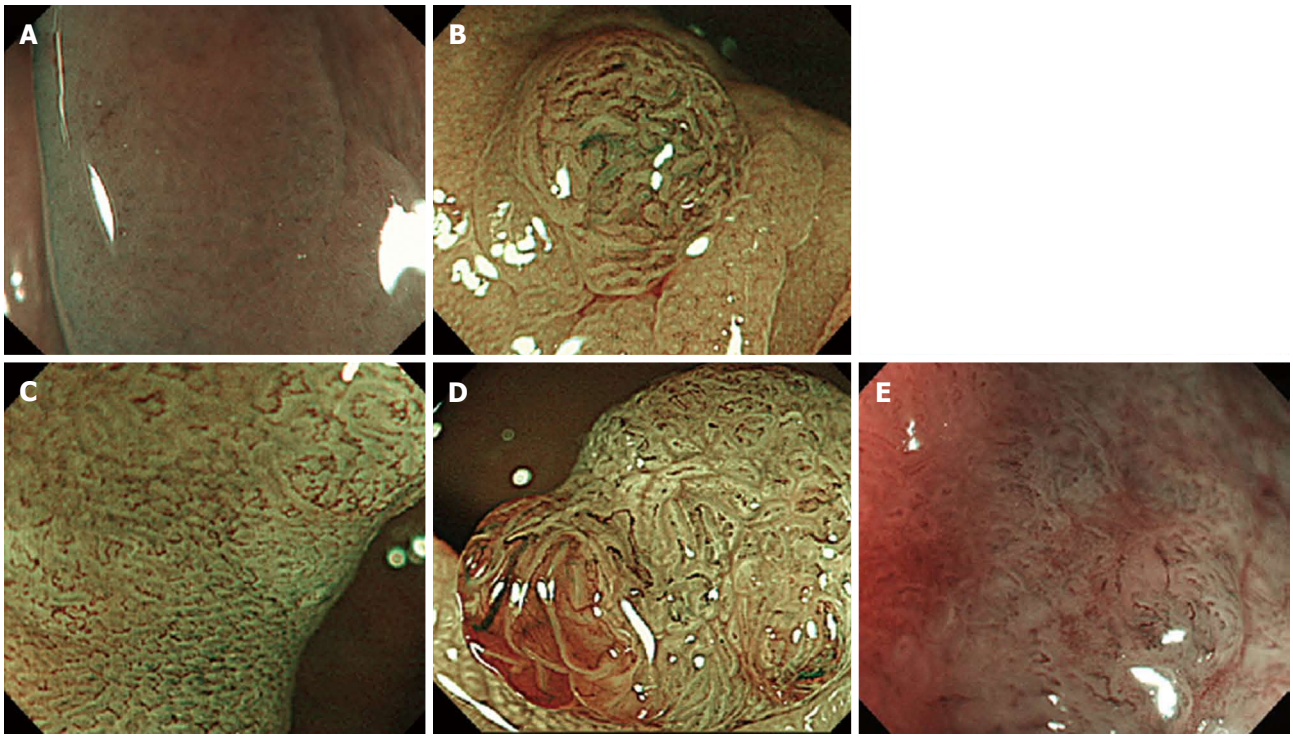

Figure 5 Narrow band imaging classification. A: Capillary pattern (CP) type Ⅰ in Sano classification. Type A in Hiroshima classification; B: CP type Ⅱ in Sano classification. Type B in Hiroshima classification; C: CP type ⅢA in Sano classification. Type C1 in Hiroshima classification; D: CP type ⅢB in Sano classification. Type C2 in Hiroshima classification; E: CP type ⅢB in Sano classification. Type C3 in Hiroshima classification.

report, type C1 is observed 46.7% in adenoma, 42.2% in intramucosal cancer, and 11.1% in massively invaded submucosal cancer[16]. In type C2, microvessels form an irregular network, surface patterns observed *via* the microvessels are irregular, and vessel diameter or distribution is heterogeneous (Figure 5D). Type C2 is observed 45.5% in intramucosal cancer and 54.5% in massively invaded submucosal cancer (Figure 6). In type C3, surface patterns *via* the microvessels are invisible, irregular vessel diameter is thick, or the vessel distribution is heterogeneous, and avascular areas are observed (Figure 5E). Type C3 is mainly observed in massively invaded submucosal cancer (Figure 6).

Showa classification

Showa classification has been divided into six groups according to endoscopical vascular features: normal, faint, network, dense, irregular and sparse. Most hyperplastic polyps show a faint pattern. The vascular patterns of adenomas are mainly network or dense ones. The predominant vascular patterns of cancer are irregular and sparse. Indeed, irregular pattern has found to be characteristic for protruded or flat-elevated cancer, whereas sparse pattern is unique to depressed cancer. Irregular or sparse pattern is observed in intramucosal cancer and adenoma (37%), and massively invaded submucosal cancer (63%) (Figure 6)[35].

Papillary and tubular patterns with in the vascular pattern

Variations are seen within the vascular pattern in neoplastic lesions. The two most important two vascular patterns, the papillary and the tubular pattern are shown. The papillary pattern shows thicker and more widening than the tubular pattern (Figure 7A). The tubular pattern shows a honeycomb-like network (Figure 7B). The

Histopathological diagnosis	Hyperplastic polyp	Adenoma Intramucosal cancer Slightly submucosal invasive cancer	Massively invaded submucosal cancer
Therapy	No therapy	Endoscopic resection	Surgical operation
Sano classification	Type Ⅰ	Type Ⅱ Type ⅢA	Type ⅢB
Hiroshima classification	Type A	Type B Type C1	Type C3 Type C2
Showa classification	Faint pattern	Dense pattern Network pattern	Sparse pattern Irregular pattern

Figure 6 The various narrow band imaging classifications and histopathological diagnoses. Classification of suspect histopathological diagnoses and therapy according to the pattern diagnosed.

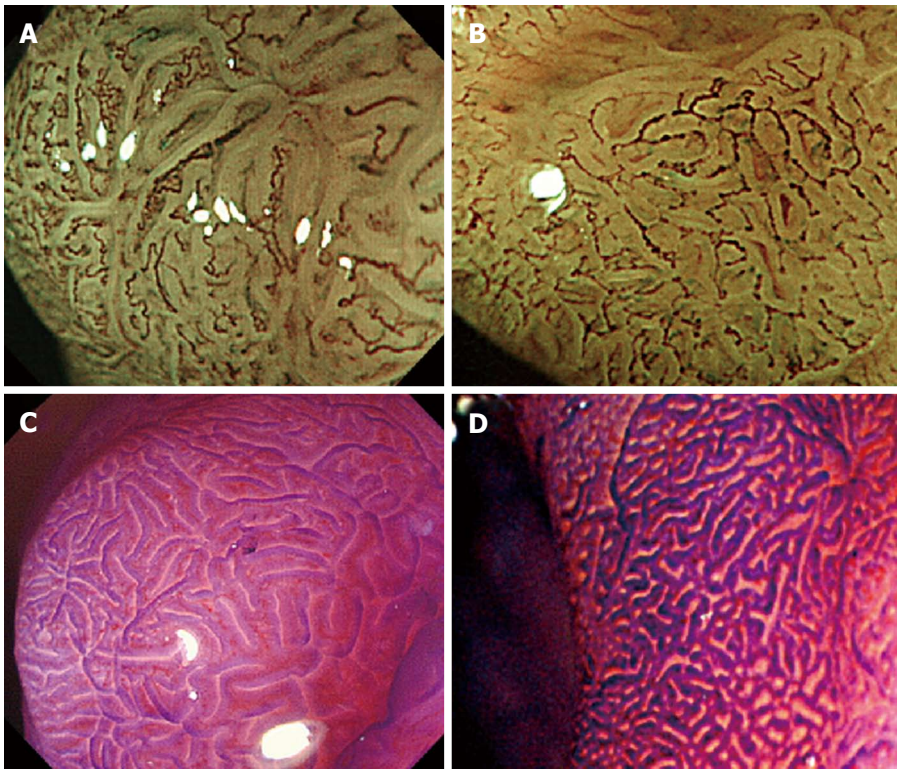

Figure 7 Papillary pattern and tubular pattern in vascular pattern. A: Papillary type. Papillary pattern is thicker and more winding than the tubular pattern. The surface pattern shows a regular pattern like the Ⅳ pit structure according to Hiroshima classification. The pattern was diagnosed type B in Sano classification, type B in Hiroshima classification, Network in Showa classification; B: Tubular type. Tubular pattern shows a regular honeycomb-like network. The surface pattern shows a regular pattern according to Hiroshima classification. The pattern was diagnosed type B in Sano classification, type B in Hiroshima classification, Network in Showa classification; C: The pit pattern classification using crystal violet showed Ⅳ pit. The histopathological diagnosis of these two patterns shows tubular adenoma; D: The pit pattern classification using crystal violet showed ⅢL pit mainly and Ⅳ pit partially. The histopathological diagnosis of these two patterns indicated tubular adenoma.

irregularity of the papillary pattern seems to be greater than that of tubular pattern. However, the surface patterns of these lesions shows a regular pattern according to the Hiroshima classification. The pits of the lesions with these patterns showed adenoma characteristics (Figure 7C, D). In addition, the histopathological diagnosis of these two patterns indicates tubular adenoma. Lesions with the papillary pattern have to be diagnosed carefully taking into account their surface pattern.

Adenoma detection rate

Colonoscopy is considered to be the standard examination against which the sensitivity of other colorectal cancer screening tests is compared[42,43]. However, polyp miss rates during colonoscopy have been evaluated in several studies[44-46]. A meta-analysis of six studies revealed that the miss rate for polyps of any size was 22%[44]. This study also demonstrated that the adenoma miss rate was 2%, 13%, and 26% for polyp sizes of 10 mm and higher, 5-10 mm and 1-5 mm respectively[44]. Another study showed that sessile or flat polyps were significantly associated with a higher miss rate[45]. The reasons for missing polyps were considered to be the quality of bowel preparation, lesion characteristics (location, number, morphology and size), the endoscopist's experience, the endoscopist's insertion and the withdrawal technique[45-48]. Many clinical studies including randomized controlled studies into the effect of NBI on improvement of miss rate in

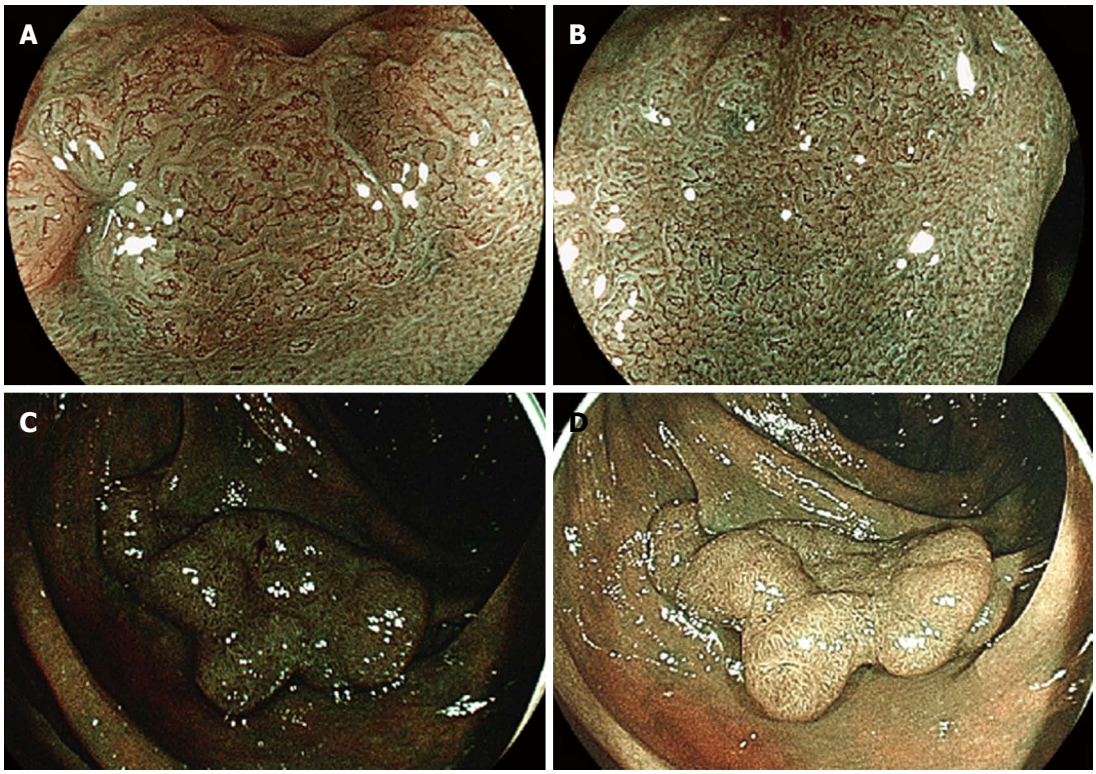

Figure 8 Blue laser imaging. A: Blue laser imaging (BLI) mode. Clear vascular patterns and the surface pattern can be seen; B: BLI mode. Clear vascular patterns and the surface pattern can be seen; C: BLI mode is slightly dark; D: BLI-bright mode is brighter than BLI mode.

colonoscopy have been reported[48-57]. In conclusion, the efficacy of NBI has been mainly unsatisfactory. One positive study by Inoue *et al*[56] demonstrated that there was a significantly higher number of adenomas detected with pancolonic NBI (22%) *vs* WL (14%), including higher number of diminutive (< 5 mm) adenomas. Moreover, the one controlled randomized study, performed in selected patients undergoing colonoscopy for colorectal screening, suggested that NBI seems to improve the detection of flat adenoma[57].

On the other hand, one negative study for NBI by Rex *et al*[51] showed that there were no differences between the NBI and WL groups in either the prevalence of adenomas or the total number of adenomas detected. Ikematsu *et al*[58] reported a Japanese multicenter prospective trial about adenoma detection rates of NBI (42.3%) and WL (42.5%) in right colon endoscopy screening. They concluded that NBI did not improve the adenoma detection rate. However, they also showed that the adenoma miss rate was significantly less with NBI (31.3%) than WL (27.8%) ($P < 0.05$). Analysis of flat and depressed lesions was performed in this study and detection rates of these lesions were not significantly different between NBI and WL.

A recent meta-analysis revealed that there was no statistically significant difference in the rates of adenoma detection rate between NBI and WL[59]. Moreover, one systemic review including 8 randomized controlled studies showed that NBI did not improve detection of colorectal polyps when compared to WL[60]. However, withdrawal time is associated with these studies. Some studies showed longer withdrawal time in NBI observation because the NBI image was dark at some distance from the polyps. If the withdrawal time is similar, the WL group might have a better adenoma detection rate during the withdrawal phase compared to that of the NBI group[60]. This may have led to the finding of significantly greater number of polyps in the WL group. In addition, poor bowel preparation made performance of the NBI visualization poorer[60]. Moreover, the use of a variety of endoscopic systems, such as the LUCERA series and EXERA-Ⅱ, may have had some impact on NBI findings. Uraoka *et al*[55] demonstrated that there are significant differences in the detection of adenomas between the sequential LUCERA series used in Japan and the simultaneous EXERA-Ⅱ series produced in Europe and America.

Three studies on FICE in the detection of neoplastic polyps have been reported[61-63]. One study showed that the detection of polyps was not significantly different between FICE and chromoendoscopy 7[61]. Two RCTs also showed that any objective improvement of FICE was not correlated with the adenoma detection rate[62,63]. On the other hand, FICE systems have been improved recently and the combination of recent systems with endoscopy allow high resolution, providing better contrast for vascular and surface patterns in magnifying endoscopy than previous FICE systems offered. Further multicenter RCT should be expected to evaluate the capability of adenoma detection in FICE.

NOVEL IEE

A new endoscope system, "EXERA Ⅲ" has been developed by Olympus. The NBI in this system delivers significantly increased brightness and contrast. This improved brightness may open new possibilities for polyp detection. Moreover, it allows "dual focus", a unique system based upon an innovative two-stage optical system enabling the user to switch between two focus settings. "Near mode" features ground breaking resolution power for close mucosal observation and "Normal mode" allows normal observation. On the other hand, a new endoscope system, "LASEREO", developed by Fujifilm, uses a semiconductor laser as a light source. The LASEREO system has two lasers, with wavelengths of 415 nm and 450 nm. The "blue laser image (BLI)", which functions as a narrow-band light and is consisted of the combination of two lasers and fluorescent light, is useful for acquiring mucosal surface information including surface blood vessel and structure patterns (Figure 8A, B). By controlling the power of the two lasers, a BLI-bright mode is set by an appropriate combination of WL and BLI light. This mode is brighter than the BLI mode alone, and it can be useful for tumor detection and observation of whole tumors (Figure 8C, D).

REFERENCES

1 **Vogelstein B**, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988; **319**: 525-532

2 **Saito Y**, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg Endosc* 2010; **24**: 343-352

3 **Kudo S**, Tamegai Y, Yamano H, Imai Y, Kogure E, Kashida H. Endoscopic mucosal resection of the colon: the Japanese technique. *Gastrointest Endosc Clin N Am* 2001; **11**: 519-535

4 **Yoshida N**, Yagi N, Naito Y, Yoshikawa T. Safe procedure in endoscopic submucosal dissection for colorectal tumors focused on preventing complications. *World J Gastroenterol* 2010; **16**: 1688-1695

5 **Rastogi A**, Keighley J, Singh V, Callahan P, Bansal A, Wani S, Sharma P. High accuracy of narrow band imaging without magnification for the real-time characterization of polyp histology and its comparison with high-definition white light colonoscopy: a prospective study. *Am J Gastroenterol* 2009; **104**: 2422-2430

6 **Togashi K**, Osawa H, Koinuma K, Hayashi Y, Miyata T, Sunada K, Nokubi M, Horie H, Yamamoto H. A comparison of conventional endoscopy, chromoendoscopy, and the optimal-band imaging system for the differentiation of neoplastic and non-neoplastic colonic polyps. *Gastrointest Endosc* 2009; **69**: 734-741

7 **Pohl J**, Nguyen-Tat M, Pech O, May A, Rabenstein T, Ell C. Computed virtual chromoendoscopy for classification of small colorectal lesions: a prospective comparative study. *Am J Gastroenterol* 2008; **103**: 562-569

8 **Kudo S**, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyuu A. Colorectal tumours and pit pattern. *J Clin Pathol* 1994; **47**: 880-885

9 **Tobaru T**, Mitsuyama K, Tsuruta O, Kawano H, Sata M. Sub-classification of type VI pit patterns in colorectal tumors: relation to the depth of tumor invasion. *Int J Oncol* 2008; **33**: 503-508

10 **Fu KI**, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T, Okuno T, Yoshida S, Fujimori T. Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. *Endoscopy* 2004; **36**: 1089-1093

11 **Konishi K**, Kaneko K, Kurahashi T, Yamamoto T, Kushima M, Kanda A, Tajiri H, Mitamura K. A comparison of magnifying and nonmagnifying colonoscopy for diagnosis of colorectal polyps: A prospective study. *Gastrointest Endosc* 2003; **57**: 48-53

12 **Machida H**, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. *Endoscopy* 2004; **36**: 1094-1098

13 **Horimatsu T**, Sano Y, Kaneko K, Ikematsu H, Katagiri A, Yano T, Fu KI, Muto M, Fujii S, Ochiai A, Yoshida S. Relationship between MVD and meshed-capillaries using magnifying NBI colonoscopy in colorectal precursor lesions. *Hepatogastroenterology* 2009; **56**: 372-377

14 **Sano Y**, Ikematsu H, Fu KI, Emura F, Katagiri A, Horimatsu T, Kaneko K, Soetikno R, Yoshida S. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. *Gastrointest Endosc* 2009; **69**: 278-283

15 **Ikematsu H**, Matsuda T, Emura F, Saito Y, Uraoka T, Fu KI, Kaneko K, Ochiai A, Fujimori T, Sano Y. Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. *BMC Gastroenterol* 2010; **10**: 33

16 **Kanao H**, Tanaka S, Oka S, Hirata M, Yoshida S, Chayama K. Narrow-band imaging magnification predicts the histology and invasion depth of colorectal tumors. *Gastrointest Endosc* 2009; **69**: 631-636

17 **Tanaka S**, Sano Y. Aim to unify the narrow band imaging (NBI) magnifying classification for colorectal tumors: current status in Japan from a summary of the consensus symposium in the 79th Annual Meeting of the Japan Gastroenterological Endoscopy Society. *Dig Endosc* 2011; **23** Suppl 1: 131-139

18 **Miyake Y**, Sekiya T, Kubo S, Hara T. A new Spectrophotometer for Measuring the Spectral Reflectance of Gastric Mucous Membrane. *J Photographic Science* 1989; **37**: 134-138

19 **Yoshida N**, Naito Y, Inada Y, Kugai M, Inoue K, Uchiyama K, Handa O, Takagi T, Konishi H, Yagi N, Morimoto Y, Wakabayashi N, Yanagisawa A, Yoshikawa T. The detection of surface patterns by flexible spectral imaging color enhancement without magnification for diagnosis of colorectal polyps. *Int J Colorectal Dis* 2012; **27**: 605-611

20 **dos Santos CE**, Lima JC, Lopes CV, Malaman D, Salomão AD, Garcia AC, Teixeira CR. Computerized virtual chromoendoscopy versus indigo carmine chromoendoscopy combined with magnification for diagnosis of small colorectal lesions: a randomized and prospective study. *Eur J Gastroenterol Hepatol* 2010; **22**: 1364-1371

21 **Parra-Blanco A**, Jiménez A, Rembacken B, González N, Nicolás-Pérez D, Gimeno-García AZ, Carrillo-Palau M, Matsuda T, Quintero E. Validation of Fujinon intelligent chromoendoscopy with high definition endoscopes in colonoscopy. *World J Gastroenterol* 2009; **15**: 5266-5273

22 **Yoshida N**, Naito Y, Kugai M, Inoue K, Uchiyama K, Takagi T, Ishikawa T, Handa O, Konishi H, Wakabayashi N, Kokura S, Yagi N, Morimoto Y, Yanagisawa A, Yoshikawa T. Efficacy of magnifying endoscopy with flexible spectral imaging color enhancement in the diagnosis of colorectal tumors. *J Gastroenterol* 2011; **46**: 65-72

23 **Matsuda T**, Saito Y, Fu KI, Uraoka T, Kobayashi N, Nakajima T, Ikehara H, Mashimo Y, Shimoda T, Murakami Y, Parra-Blanco A, Fujimori T, Saito D. Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate?--a pilot study. *Am J Gastroenterol* 2008; **103**: 1926-1932

24 **Takeuchi Y**, Uedo N, Higashino K, Ishihara R, Tatsuta M, Iishi H, Matsumura M. Autofluorescence imaging of a diminutive, depressed-type early colon cancer invaded to the submucosal layer. *Gastrointest Endosc* 2010; **71**: 399-400; discussion 400

25 **McCallum AL**, Jenkins JT, Gillen D, Molloy RG. Evaluation of autofluorescence colonoscopy for the detection and diagnosis of colonic polyps. *Gastrointest Endosc* 2008; **68**: 283-290

26 **Tischendorf JJ**, Schirin-Sokhan R, Streetz K, Gassler N, Hecker HE, Meyer M, Tacke F, Wasmuth HE, Trautwein C, Winograd R. Value of magnifying endoscopy in classifying colorectal polyps based on vascular pattern. *Endoscopy* 2010; **42**: 22-27

27 **Henry ZH**, Yeaton P, Shami VM, Kahaleh M, Patrie JT, Cox DG, Peura DA, Emura F, Wang AY. Meshed capillary vessels found on narrow-band imaging without optical magnification effectively identifies colorectal neoplasia: a North American validation of the Japanese experience. *Gastrointest Endosc* 2010; **72**: 118-126

28 **Rex DK**. Narrow-band imaging without optical magnification for histologic analysis of colorectal polyps. *Gastroenterology* 2009; **136**: 1174-1181

29 **Su MY**, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. *Am J Gastroenterol* 2006; **101**: 2711-2716

30 **Longcroft-Wheaton GR**, Higgins B, Bhandari P. Flexible spectral imaging color enhancement and indigo carmine in neoplasia diagnosis during colonoscopy: a large prospective UK series. *Eur J Gastroenterol Hepatol* 2011; **23**: 903-911

31 **Kim YS**, Kim D, Chung SJ, Park MJ, Shin CS, Cho SH, Kim JS, Song IS. Differentiating small polyp histologies using real-time screening colonoscopy with Fuji Intelligent Color Enhancement. *Clin Gastroenterol Hepatol* 2011; **9**: 744-749.e1

32 **Ignjatovic A**, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. *Lancet Oncol* 2009; **10**: 1171-1178

33 **Takeuchi Y**, Inoue T, Hanaoka N, Higashino K, Iishi H, Chatani R, Hanafusa M, Kizu T, Ishihara R, Tatsuta M, Shimokawa T, Uedo N. Autofluorescence imaging with a transparent hood for detection of colorectal neoplasms: a prospective, randomized trial. *Gastrointest Endosc* 2010; **72**: 1006-1013

34 **Sato R**, Fujiya M, Watari J, Ueno N, Moriichi K, Kashima S, Maeda S, Ando K, Kawabata H, Sugiyama R, Nomura Y, Nata T, Itabashi K, Inaba Y, Okamoto K, Mizukami Y, Saitoh Y, Kohgo Y. The diagnostic accuracy of high-resolution endoscopy, autofluorescence imaging and narrow-band imaging for differentially diagnosing colon adenoma. *Endoscopy* 2011; **43**: 862-868

35 **Wada Y**, Kashida H, Kudo SE, Misawa M, Ikehara N, Hamatani S. Diagnostic accuracy of pit pattern and vascular pattern analyses in colorectal lesions. *Dig Endosc* 2010; **22**: 192-199

36 **Katagiri A**, Fu KI, Sano Y, Ikematsu H, Horimatsu T, Kaneko K, Muto M, Yoshida S. Narrow band imaging with magnifying colonoscopy as diagnostic tool for predicting histology of early colorectal neoplasia. *Aliment Pharmacol Ther* 2008; **27**: 1269-1274

37 **Singh R**, Nordeen N, Mei SL, Kaffes A, Tam W, Saito Y. West meets East: preliminary results of narrow band imaging with optical magnification in the diagnosis of colorectal lesions: a multicenter Australian study using the modified Sano's classification. *Dig Endosc* 2011; **23** Suppl 1: 126-130

38 **Saito S**, Tajiri H, Ohya T, Nikami T, Aihara H, Ikegami M. Imaging by Magnifying Endoscopy with NBI Implicates the Remnant Capillary Network As an Indication for Endoscopic Resection in Early Colon Cancer. *Int J Surg Oncol* 2011; **2011**: 242608

39 **Fukuzawa M**, Saito Y, Matsuda T, Uraoka T, Itoi T, Moriyasu F. Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer. *World J Gastroenterol* 2010; **16**: 1727-1734

40 **Higashi R**, Uraoka T, Kato J, Kuwaki K, Ishikawa S, Saito Y, Matsuda T, Ikematsu H, Sano Y, Suzuki S, Murakami Y, Yamamoto K. Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program. *Gastrointest Endosc* 2010; **72**: 127-135

41 **Raghavendra M**, Hewett DG, Rex DK. Differentiating adenomas from hyperplastic colorectal polyps: narrow-band imaging can be learned in 20 minutes. *Gastrointest Endosc* 2010; **72**: 572-576

42 **Whitlock EP**, Lin J, Liles E, Beil T, Fu R, O'Connor E, Thompson RN, Cardenas T. Screening for Colorectal Cancer: An Updated Systematic Review [Internet]. Rockville: Agency for Healthcare Research and Quality, 2008

43 **Whitlock EP**, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2008; **149**: 638-658

44 **van Rijn JC**, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol* 2006; **101**: 343-350

45 **Heresbach D**, Barrioz T, Lapalus MG, Coumaros D, Bauret P, Potier P, Sautereau D, Boustière C, Grimaud JC, Barthélémy C, Sée J, Serraj I, D'Halluin PN, Branger B, Ponchon T. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. *Endoscopy* 2008; **40**: 284-290

46 **Postic G**, Lewin D, Bickerstaff C, Wallace MB. Colonoscopic miss rates determined by direct comparison of colonoscopy with colon resection specimens. *Am J Gastroenterol* 2002; **97**: 3182-3185

47 **Morini S**, Hassan C, Zullo A, Lorenzetti R, de Matthaeis M, Stella F, Campo SM. Detection of colonic polyps according to insertion/withdrawal phases of colonoscopy. *Int J Colorectal Dis* 2009; **24**: 527-530

48 **Pickhardt PJ**, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. *Ann Intern Med* 2004; **141**: 352-359

49 **Adler A**, Pohl H, Papanikolaou IS, Abou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rösch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? *Gut* 2008; **57**: 59-64

50 **Adler A**, Aschenbeck J, Yenerim T, Mayr M, Aminalai A, Drossel R, Schröder A, Scheel M, Wiedenmann B, Rösch T. Narrow-band versus white-light high definition television endoscopic imaging for screening colonoscopy: a prospective randomized trial. *Gastroenterology* 2009; **136**: 410-416.e1; quiz 715

51 **Rex DK**, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. *Gastroenterology* 2007; **133**: 42-47

52 **Kaltenbach T**, Friedland S, Soetikno R. A randomised tandem colonoscopy trial of narrow band imaging versus white light examination to compare neoplasia miss rates. *Gut* 2008; **57**: 1406-1412

53 **Rastogi A**, Bansal A, Wani S, Callahan P, McGregor DH,

Cherian R, Sharma P. Narrow-band imaging colonoscopy--a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. *Gastrointest Endosc* 2008; **67**: 280-286

54 **East JE**, Ignjatovic A, Suzuki N, Guenther T, Bassett P, Tekkis PP, Saunders BP. A randomized, controlled trial of narrow-band imaging vs high-definition white light for adenoma detection in patients at high risk of adenomas. *Colorectal Dis* 2012; **14**: e771-e778

55 **Uraoka T**, Saito Y, Matsuda T, Sano Y, Ikehara H, Mashimo Y, Kikuchi T, Saito D, Saito H. Detectability of colorectal neoplastic lesions using a narrow-band imaging system: a pilot study. *J Gastroenterol Hepatol* 2008; **23**: 1810-1815

56 **Inoue T**, Murano M, Murano N, Kuramoto T, Kawakami K, Abe Y, Morita E, Toshina K, Hoshiro H, Egashira Y, Umegaki E, Higuchi K. Comparative study of conventional colonoscopy and pan-colonic narrow-band imaging system in the detection of neoplastic colonic polyps: a randomized, controlled trial. *J Gastroenterol* 2008; **43**: 45-50

57 **Paggi S**, Radaelli F, Amato A, Meucci G, Mandelli G, Imperiali G, Spinzi G, Terreni N, Lenoci N, Terruzzi V. The impact of narrow band imaging in screening colonoscopy: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2009; **7**: 1049-1054

58 **Ikematsu H**, Saito Y, Tanaka S, Uraoka T, Sano Y, Horimatsu T, Matsuda T, Oka S, Higashi R, Ishikawa H, Kaneko K. The impact of narrow band imaging for colon polyp detection: a multicenter randomized controlled trial by tandem colonoscopy. *J Gastroenterol* 2012; **47**: 1099-1107

59 **Jin XF**, Chai TH, Shi JW, Yang XC, Sun QY. Meta-analysis for evaluating the accuracy of endoscopy with narrow band imaging in detecting colorectal adenomas. *J Gastroenterol Hepatol* 2012; **27**: 882-887

60 **Sabbagh LC**, Reveiz L, Aponte D, de Aguiar S. Narrow-band imaging does not improve detection of colorectal polyps when compared to conventional colonoscopy: a randomized controlled trial and meta-analysis of published studies. *BMC Gastroenterol* 2011; **11**: 100

61 **Pohl J**, Lotterer E, Balzer C, Sackmann M, Schmidt KD, Gossner L, Schaab C, Frieling T, Medve M, Mayer G, Nguyen-Tat M, Ell C. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. *Gut* 2009; **58**: 73-78

62 **Aminalai A**, Rösch T, Aschenbeck J, Mayr M, Drossel R, Schröder A, Scheel M, Treytnar D, Gauger U, Stange G, Simon F, Adler A. Live image processing does not increase adenoma detection rate during colonoscopy: a randomized comparison between FICE and conventional imaging (Berlin Colonoscopy Project 5, BECOP-5). *Am J Gastroenterol* 2010; **105**: 2383-2388

63 **Chung SJ**, Kim D, Song JH, Park MJ, Kim YS, Kim JS, Jung HC, Song IS. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointest Endosc* 2010; **72**: 136-142

S- Editor Song XX **L- Editor** Hughes D **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.556

World J Gastrointest Endosc 2012 December 16; 4(12): 556-560
ISSN 1948-5190 (online)

BRIEF ARTICLE

Efficacy of ankaferd blood stopper application on non-variceal upper gastrointestinal bleeding

Gokhan Gungor, M Hakan Goktepe, Murat Biyik, Ilker Polat, Tuncer Tuna, Huseyin Ataseven, Ali Demir

Gokhan Gungor, Selcuk University, Meram School of Medicine, Gastroenterology Department, Meram, 42080 Konya, Turkey
M Hakan Goktepe, Ilker Polat, Tuncer Tuna, Selcuk University Meram Faculty of Medicine, Internal Medicine Konya, 42080 Konya, Turkey
Murat Biyik, Huseyin Ataseven, Ali Demir, Selcuk University Meram Faculty of Medicine, Gastroenterology, 42080 Konya, Turkey
Author contributions: Gungor G, Goktepe MH and Polat I performed the majority of experiments; Biyik M and Tuna T helped to write the article and did the language editing; Ataseven H and Demir A designed the study.
Correspondence to: Gokhan Gungor, MD, Selcuk University, Meram School of Medicine, Gastroenterology Department, Meram, 42080 Konya, Turkey. drgokhangungor@hotmail.com
Telephone: +90-332-2237121 Fax: +90-332-2237121
Received: December 23, 2011 Revised: September 5, 2012
Accepted: October 20, 2012
Published online: December 16, 2012

Abstract

AIM: To prospectively assess the hemostatic efficacy of the endoscopic topical use of ankaferd blood stopper (ABS) in active non-variceal upper gastrointestinal system (GIS) bleeding.

METHODS: Endoscopy was performed on 220 patients under suspiciency of GIS bleeding. Patients with active non-variceal upper gastrointestinal bleeding (NVUGIB) with a spurting or oozing type were included. Firstly, 8-10 cc of isotonic saline was sprayed to bleeding lesions. Then, 8 cc of ABS was applied on lesions in which bleeding continued after isotonic saline application. The other endoscopic therapeutic methods were applied on the lesions in which the bleeding did not stop after ABS.

RESULTS: Twenty-seven patients had an active NVUGIB with a spurting or oozing type and 193 patients were excluded from the study since they did not have non-variceal active bleeding. 8 cc of ABS was sprayed on to the lesions of 26 patients whose bleeding continued after isotonic saline and in 19 of them, bleeding stopped after ABS. Other endoscopic treatment methods were applied to the remaining patients and the bleeding was stopped with these interventions in 6 of 7 patients.

CONCLUSION: ABS is an effective method on NVUGIB, particularly on young patients with no coagulopathy. ABS may be considered as part of a combination treatment with other endoscopic methods.

Key words: Ankaferd blood stopper; Non-variceal upper gastrointestinal bleeding; Endoscopic treatment

Peer reviewer: Naoki Muguruma, MD, PhD, Department of Gastroenterology and Oncology, the University of Tokushima Graduate School, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan

Gungor G, Goktepe MH, Biyik M, Polat I, Tuna T, Ataseven H, Demir A. Efficacy of ankaferd blood stopper application on non-variceal upper gastrointestinal bleeding. *World J Gastrointest Endosc* 2012; 4(12): 556-560 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/556.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.556

INTRODUCTION

Upper gastrointestinal system (GIS) bleeding is a frequently seen emergent situation with a mortality of about 7%-10%[1]. This rate may increase with concomitant comorbid diseases.

Endoscopy is the gold-standard technique in the diagnosis of gastrointestinal bleeding. It provides important information about the bleeding point, its localization, the amount of bleeding and risk for re-bleeding. Active

bleeding may be stopped with therapeutic applications and the risk of re-bleeding may be reduced. Endoscopic treatment methods are indicated in lesions with active bleeding and with a visible vessel[2]. Endoscopic treatment may be disputable for lesions with a blood clot; however, the data of recent years demonstrate that it may be effective to apply endoscopic treatment for these lesions rather than to observe them[3]. Endoscopic treatment is not necessary for a clean-based ulcer since the re-bleeding risk is minimal[2]. Injection treatments, cauterization methods and mechanical therapies are the major endoscopic treatment modalities[4].

In recent years, it was reported that ankaferd blood stopper (ABS), of which each 100 milliliter of folkloric liquid product contains a standard mixture of 5 mg of Thymus Vulgaris (thyme-dried herbal extract), 9 mg of Glycyrrhiza Glabra (licorice-dried leaf extract), 8 mg of Vitis Vinifera (grape-dried leaf extract), 7 mg of Alpinia Officinarum (lesser galangal-dried leaf extract) and 6 mg of Urtica Dioica (stinging nettle-dried root extract), forms a system by precipitating fibrinogen and forming a protein network which acts as an anchor for vital physiological erythrocyte aggregation, covering the classical cascade model of the clotting system, independently acting on coagulation factors and platelets in blood and serum. It was also reported that it provides this effect in milliseconds in *in vitro* conditions and seconds in *in vivo* conditions. The topical use of ABS has been approved by the Turkish Ministry of Health for the management of dermal, external post-surgical and post-dental surgery bleeding[5].

It was reported that ABS was applied on bleeding lesions of GIS malignancies[6,7], peptic ulcers[8], fundal varices[9], dieulafoy lesions[10,11], radiation colitis[12], rectal ulcers[13] and non-variceal upper gastrointestinal bleeding (NVUGIB)[14]. Most of the bleeding lesions were controlled in all patient groups. However, controlled trials are not available about this topic.

We researched the efficacy of ABS application with a spray catheter on active NVUGIB lesions.

MATERIALS AND METHODS

Endoscopy was performed on 220 patients under suspiciency of GIS bleeding within 12 h of admission to Selcuk University, Meram Faculty of Medicine, between April 2009 and August 2010, after approval of the local ethics committee. All volunteers gave written informed consent. Twenty-seven patients with active spurting or oozing type NVUGIB were included in the study and 193 patients without these conditions were excluded. Firstly, 8-10 cc of isotonic saline was sprayed on to the bleeding lesions. 8 cc of ABS was applied with a Medi-Globe® spray catheter on lesions in which bleeding continued after isotonic saline application. Air was applied with an injector to the catheter after ABS application and the product was completely discharged from the catheter. The other endoscopic hemostatic methods (injection treatment, hemoclip, electro-coagulation, heater probe, Argon Plasma Coagulation) were applied on the lesions in which the bleeding did not stop within one minute after ABS application. They were then observed for re-bleeding. The control endoscopy was performed approximately 48 h after the first endoscopy. Also, we treated all patients during admission and at the time of discharge with specific medical therapies (such as proton pump inhibitors, transfusion, intravenous hydration, other co-mobidity drugs).

RESULTS

Characteristics of patients

Endoscopy was performed on 220 patients with suspiciency of NVUGIB. Twenty-seven of these patients had NVUGIB with a spurting or oozing type. 193 patients were excluded from the study since they did not have non-variceal active bleeding. In most of these 193 patients, in endoscopy, bleeding was stopped or there was hematinized blood in the stomach, visible vessel or blood clot stuck on their lesions. Ten patients (37%) were women, 17 (63%) men and the mean age was 59.1% ± 17%. 70% of all patients (19 patients) had co-morbid diseases. Two patients had chronic obstructive lung diseases, 2 a mitral valve replacement, 2 chronic renal failure, 2 malignancy, 1 liver cirrhosis, 1 atrial fibrillation, 1 coronary artery disease and 4 patients had a history of gastric surgery. Twelve patients had a GIS bleeding history. It was observed that 46% of patients complained of melena, 38.4% hematemesis and melena, 7.7% hematemesis and 7.4% malaise, anemia and other complaints.

Results of endoscopic applications

Firstly, 8 cc isotonic saline was sprayed on to bleeding lesions. The bleeding was stopped in one patient after isotonic saline application but re-bleeding was observed during the follow up.

8 cc of ABS was sprayed to the lesions of 26 patients whose bleeding continued after isotonic saline and bleeding was stopped in 19 of these 26 patients after ABS. Images of endoscopic ABS application are shown in Figures 1 and 2.

The other endoscopic methods could not be applied to 1 of 7 patients whose bleeding continued after ABS since the bleeding was a widespread mucosal oozing type. The other endoscopic treatment methods in addition to ABS were applied to the remaining 6 patients (argon plasma coagulation, injection sclerotherapy, hemoclip) and it was observed that the bleeding stopped with these interventions on all patients.

It is not ethical to form only one placebo group of active bleeding patients. It was statistically significant that ABS only and ABS + other methods are superior to stop the bleeding when isotonic saline application is considered as an ineffective placebo (McNemar test, for each $P = 0.001$) and no statistically significant difference was observed between ABS only and ABS + classical methods.

The rate of re-bleeding was 15.8% in patients whose

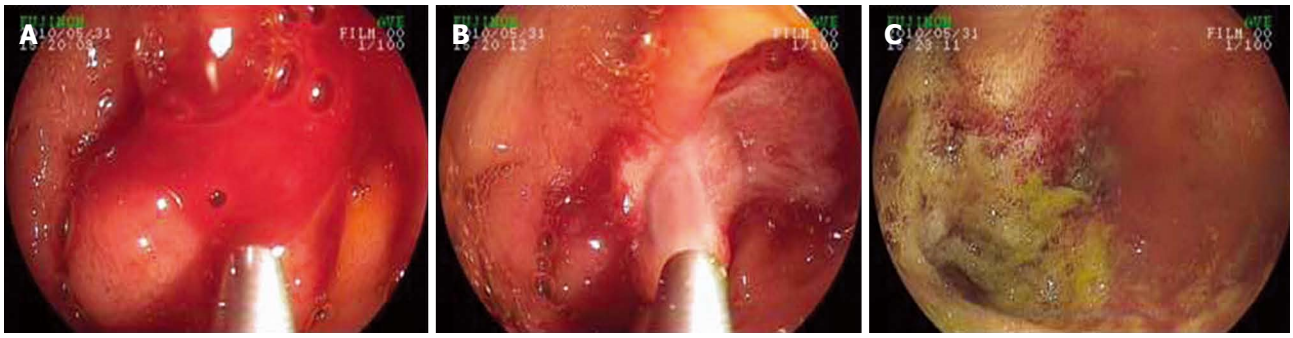

Figure 1 Ankaferd blood stopper application on an oozing type bleeding lesion. A: Oozing type bleeding; B: Ankaferd blood stopper (ABS) is being sprayed; C: ABS after ankaferd blood stopper application.

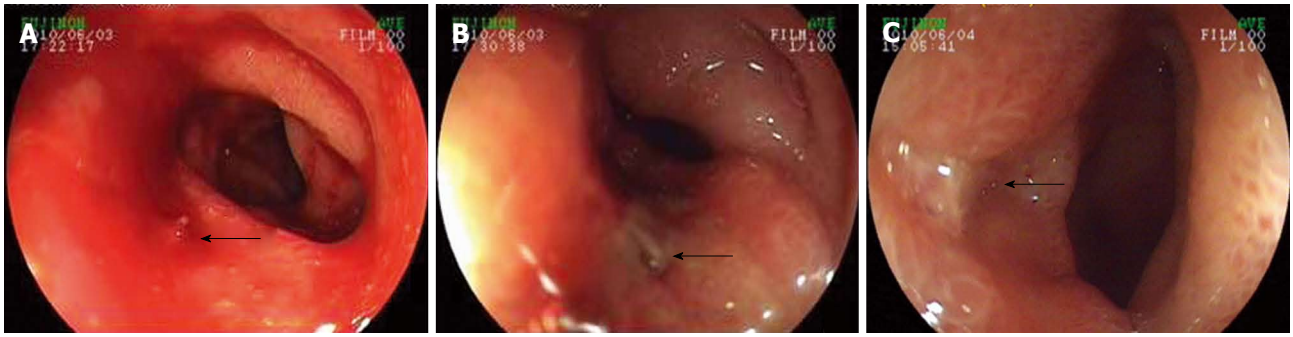

Figure 2 Ankaferd blood stopper application on a pulsatile bleeding lesion. A: Pulsatile bleeding; B: After ankaferd blood stopper application; C: Control of the lesion after 2 d.

Table 1 Results of endoscopic treatments

Endoscopic treatment	Group				
	Stopped (*n*)	Not stopped (*n*)	Re-bleeding, *n* (%)	Transfusion (unit)	Hospitalization (d)
Isotonic saline	1	26	1 (3.8)	3	1
ABS only	19	7	3 (15.8)	2.4	6
ABS + Other Methods			2 (33.3)	4.4	6.75
ABS + Adrenaline	4	0			
ABS + Adrenaline + Hemoclip	1	0			
ABS + Adrenaline + Polidocanol	1	0			

ABS: Ankaferd blood stopper.

bleeding was controlled with ABS only, 33.3% in patients whose bleeding was brought under control by applying ABS + classical methods and 20% in all patients. Results of endoscopic treatments are shown Table 1.

The effect of age and gender on bleeding control with ABS

No statistically significant difference was found in patients whose bleeding was stopped by applying ABS only in terms of age and gender.

The mean age of 19 patients whose bleeding was stopped by applying ABS was 55 and 68 in the 7 patients whose bleeding could not be stopped by applying ABS. Although this is not a statistically significant difference (Mann Whitney *U* test, $P = 0.95$), the mean age was higher in patients whose bleeding could not be stopped.

The effect of endoscopic diagnosis on bleeding control with ABS

Peptic ulcer was the most common bleeding lesion and this is compatible with the literature. The endoscopic diagnosis and results of ABS application are given in Table 2.

The effect of bleeding type on bleeding control with ABS

Patients in whom only ABS was applied were evaluated according to the bleeding type. 15.3% of them had a spurting type and 84.7% an oozing type. Bleeding control was provided with ABS on 3 of 4 patients (75%) with bleeding of a spurting type and 16 of 22 patients (72%) with bleeding of an oozing type. There was no statistically significant difference between spurting and oozing types of lesions for bleeding control with ABS

Table 2 Endoscopic diagnosis and results of all patients with ankaferd blood stopper applied

Endoscopic finding	Group		Total (*n*)
	Stopped (*n*)	Not Stopped (*n*)	
Gastric ulcer	2	1	3
Duodenal ulcer	9	3	12
Erosive ulcer	0	2	2
Esophagitis	2	0	2
Anastomosis ulcer	2	0	2
Dieulafoy lesion	1	1	2
Post-polypectomy	2	0	2
Malignancy	1	0	1
Total	19	7	26

Table 3 Use of drugs and results of ankaferd blood stopper applied patients

Drug	Group		Total (*n*)
	Stopped (*n*)	Not Stopped (*n*)	
Not taking a drug	10	2	12
ASA	3	3	6
Warfarin	1	1	2
ASA + NSAID	1	0	1
ASA + Warfarin	0	1	1
Steroid	1	0	1
Other	3	0	3
Total	19	7	26

ASA: Acetylsalicylic acid; NSAID: Non-steroidal anti-inflammatory drug.

(Fisher's Exact test, $P = 1.0$).

The effect of coagulation parameters on bleeding control with ABS

The mean thrombocyte count was 229.771/mm^3 of the 19 patients whose bleeding was stopped by applying ABS and 132.232/mm^3 of the 7 patients whose bleeding could not be stopped by applying ABS. This difference was statistically significant (independent sample test, $P = 0.005$). However, the mean INR value of 19 patients whose bleeding was controlled was 1.33 and activa partial thromboplastin time (aPTT) was 27.5 s, while the mean INR value of 7 patients whose bleeding could not be controlled was 3.07 and aPTT was 39.1 s.

If one or more of the abnormal results of thrombocyte count, PT-INR or aPTT levels were defined as coagulopathy, it was abnormal in patients whose bleeding could not be stopped with ABS application and it was statistically significant (*F*-test, $P = 0.006$).

The effect of drug use on bleeding control with ABS

The drug usage and results of the only ABS group are given in Table 3. It was observed that the bleeding of 3 of 6 patients who were taking ASA and 1 of 2 patients who were taking ASA + warfarin did not stop with applying ABS. These results demonstrated that the bleeding control with ABS was more difficult for patients who were taking ASA and/or warfarin.

DISCUSSION

There is insufficient literature that demonstrates the efficacy of ABS on gastrointestinal bleeding and the available data are mostly case reports or case series. This study is the first prospective study in which ABS is applied on non-variceal gastrointestinal system bleeding and the effects of many factors on bleeding control analyzed.

According to these results, the rate of bleeding control was 73% with ABS only, 100% with ABS in combination with classical methods and 96% with ABS only and ABS + classical methods. When isotonic saline application is considered an ineffective placebo, it was observed that ABS only and ABS + other methods are superior to placebo and statistically significant. The advanced age of patients made it difficult to control bleeding with ABS.

When the study is evaluated in terms of re-bleeding, re-bleeding was observed in 15.8% of patients whose hemostasis was provided with ABS only, 33.3% with ABS + classical methods and 20% with ABS only and ABS + classical methods. According to the literature, the rate of re-bleeding is about 100%[4] in spurting or oozing type bleedings if no endoscopic treatment is applied, 20% in adrenaline injection, 15%-20% in ablative treatment and 5%-15% in combination treatment. In this study, the rate of re-bleeding of patients with ABS only and provided hemostasis was similar to the other endoscopic methods[15-17] mentioned in the literature.

The results of this study also demonstrate that ABS application with a spray catheter may have a limited effect on bleeding control of patients with coagulopathy or using ASA and/or warfarin. In such situations, more ABS and a mechanical compress may be applied on lesions as an alternative technique or ABS may be applied on patients with other endoscopic methods, such as a combination treatment, as a different approach.

The application of ABS on lesions with a spray catheter may provide a more homogenous and effective contact with lesions compared to the application with a nasogastric catheter or tools like tubes. In addition, the contact time of ABS applied to the bleeding point may have an important role in stopping the bleeding. The methods which provide a longer contact time of ABS to the bleeding point (balloon or compression tools like a funnel) may be more useful.

In summary, these results demonstrate that the application of ABS with topical spraying for bleeding control on non-variceal upper GIS bleeding, particularly on young patients without coagulopathy, is effective. ABS may be considered as a part of combination treatment for cases with a higher re-bleeding possibility (coagulopathy, dieulafoy lesion, arterial bleeding, *etc.*)[10,11].

Randomized controlled studies are needed for the comparison of ABS application alone and in combination with other endoscopic methods (e.g., thermo-coagulation, clips or adrenaline injection).

COMMENTS

Background

Injection treatments, cauterization methods and mechanical therapies are the major endoscopic treatment modalities in active gastrointestinal bleeding. In recent years, it was reported that ankaferd blood stopper (ABS) forms a system by precipitating fibrinogen and forming a protein network which acts as an anchor for vital physiological erythrocyte aggregation, covering the classical cascade model of the clotting system, independently acting on coagulation factors and platelets in blood and serum. The authors researched the efficacy of ABS application with a spray catheter on active non-variceal upper gastrointestinal bleeding (NVUGIB) lesions.

Research frontiers

This study investigated the efficacy of a different technique in non-variceal gastrointestinal bleeding.

Related publications

It was reported that ABS was applied on bleeding lesions of gastrointestinal system (GIS) malignancies, fundal varices, dieulafoy lesions, radiation colitis, rectal ulcers and NVUGIB. Most of the bleeding lesions were controlled in all patient groups. However, controlled trials are not available about this topic.

Innovations and breakthroughs

This study demonstrates that the application of ABS with topical spraying for bleeding control on non-variceal upper GIS bleeding, particularly on young patients without coagulopathy, is effective.

Applications

The application of ABS on lesions with a spray catheter may provide a more homogenous and effective contact with lesions compared to the application with a nasogastric catheter or tools like tubes. In addition, the contact time of ABS applied to the bleeding point may have an important role in stopping the bleeding. The methods which provide a longer contact time of ABS to the bleeding point (balloon or compression tools like a funnel) may be more useful.

Terminology

Ankafeld blood stopper contains a standard mixture of 5 mg of Thymus Vulgaris (thyme-dried herbal extract), 9 mg of Glycyrrhiza Glabra (licorice-dried leaf extract), 8 mg of Vitis Vinifera (grape-dried leaf extract), 7 mg of Alpinia Officinarum (lesser galangal-dried leaf extract) and 6 mg of Urtica Dioica (stinging nettle-dried root extract) in each 100 mL of liquid folkloric product effective in coagulation.

Peer review

The application of ABS on lesions with a spray catheter may be helpful in the control of gastrointestinal bleeding alone or in combination treatment with other endoscopic methods.

REFERENCES

1 **Yavorski RT**, Wong RK, Maydonovitch C, Battin LS, Furnia A, Amundson DE. Analysis of 3,294 cases of upper gastrointestinal bleeding in military medical facilities. *Am J Gastroenterol* 1995; **90**: 568-573

2 **Johnston JH**. Endoscopic risk factors for bleeding peptic ulcer. *Gastrointest Endosc* 1990; **36**: S16-S20

3 **Bleau BL**, Gostout CJ, Sherman KE, Shaw MJ, Harford WV, Keate RF, Bracy WP, Fleischer DE. Recurrent bleeding from peptic ulcer associated with adherent clot: a randomized study comparing endoscopic treatment with medical therapy. *Gastrointest Endosc* 2002; **56**: 1-6

4 **Adler DG**, Leighton JA, Davila RE, Hirota WK, Jacobson BC, Qureshi WA, Rajan E, Zuckerman MJ, Fanelli RD, Hambrick RD, Baron T, Faigel DO. ASGE guideline: The role of endoscopy in acute non-variceal upper-GI hemorrhage. *Gastrointest Endosc* 2004; **60**: 497-504

5 **Goker H**, Haznedaroglu IC, Ercetin S, Kirazli S, Akman U, Ozturk Y, Firat HC. Haemostatic actions of the folkloric medicinal plant extract Ankaferd Blood Stopper. *J Int Med Res* 2008; **36**: 163-170

6 **Kurt M**, Akdogan M, Onal IK, Kekilli M, Arhan M, Shorbagi A, Aksu S, Kurt OK, Haznedaroglu IC. Endoscopic topical application of Ankaferd Blood Stopper for neoplastic gastrointestinal bleeding: A retrospective analysis. *Dig Liver Dis* 2010; **42**: 196-199

7 **Ozaslan E**, Purnak T, Yildiz A, Haznedaroglu IC. A new practical alternative for tumoural gastrointestinal bleeding: Ankaferd blood stopper. *Dig Liver Dis* 2010; **42**: 594-595

8 **Purnak T**, Ozaslan E, Beyazit Y, Haznedaroglu IC. Upper gastrointestinal bleeding in a patient with defective hemostasis successfully treated with ankaferd blood stopper. *Phytother Res* 2011; **25**: 312-313

9 **Tuncer I**, Doganay L, Ozturk O. Instant control of fundal variceal bleeding with a folkloric medicinal plant extract: Ankaferd Blood Stopper. *Gastrointest Endosc* 2010; **71**: 873-875

10 **Kurt M**, Kacar S, Onal IK, Akdogan M, Haznedaroglu IC. Ankaferd Blood Stopper as an effective adjunctive hemostatic agent for the management of life-threatening arterial bleeding of the digestive tract. *Endoscopy* 2008; **40** Suppl 2: E262

11 **Kurt M**, Onal I, Akdogan M, Kekilli M, Arhan M, Sayilir A, Oztas E, Haznedaroglu I. Ankaferd Blood Stopper for controlling gastrointestinal bleeding due to distinct benign lesions refractory to conventional antihemorrhagic measures. *Can J Gastroenterol* 2010; **24**: 380-384

12 **Ozaslan E**, Purnak T, Yildiz A, Akar T, Avcioglu U, Haznedaroglu IC. The effect of Ankaferd blood stopper on severe radiation colitis. *Endoscopy* 2009; **41** Suppl 2: E321-E322

13 **Ibis M**, Kurt M, Onal IK, Haznedaroglu IC. Successful management of bleeding due to solitary rectal ulcer via topical application of Ankaferd blood stopper. *J Altern Complement Med* 2008; **14**: 1073-1074

14 **Ozaslan E**, Purnak T, Yildiz A, Haznedaroglu IC. The effect of a new hemostatic agent for difficult cases of non-variceal gastrointestinal bleeding: Ankaferd blood stopper. *Hepatogastroenterology* 2010; **57**: 191-194

15 **Elta GH**. Acute Nonvariceal Upper Gastrointestinal Hemorrhage. *Curr Treat Options Gastroenterol* 2002; **5**: 147-152

16 **Kovacs TO**, Jensen DM. Endoscopic treatment of ulcer bleeding. *Curr Treat Options Gastroenterol* 2007; **10**: 143-148

17 **Llach J**, Bordas JM, Salmerón JM, Panés J, García-Pagán JC, Feu F, Navasa M, Mondelo F, Piqué JM, Mas A, Terés J, Rodés J. A prospective randomized trial of heater probe thermocoagulation versus injection therapy in peptic ulcer hemorrhage. *Gastrointest Endosc* 1996; **43**: 117-120

S- Editor Song XX **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.561

World J Gastrointest Endosc 2012 December 16; 4(12): 561-564
ISSN 1948-5190 (online)

BRIEF ARTICLE

Relationship of human rectal aberrant crypt foci and formation of colorectal polyp: One-year following up after polypectomy

Hirokazu Takahashi, Eiji Yamada, Hidenori Ohkubo, Eiji Sakai, Takuma Higurashi, Takashi Uchiyama, Kunihiro Hosono, Hiroki Endo, Atsushi Nakajima

Hirokazu Takahashi, Eiji Yamada, Hidenori Ohkubo, Eiji Sakai, Takuma Higurashi, Takashi Uchiyama, Kunihiro Hosono, Hiroki Endo, Atsushi Nakajima, Gastroenterology Division, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan
Author contributions: Takahashi H designed the study and wrote the manuscript; Yamada E, Ohkubo H, Sakai E, Higurashi T and Uchiyama T performed the colonoscopy; Hosono K and Endo H provided the collection of physical and imaging findings; Nakajima A providing appropriate advice for this work.
Supported by Grant-in-Aid for Research on the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare, Japan to Nakajima A; a grant from the National Institute of Biomedical Innovation (NBIO) to Nakajima A; a grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan (KIBAN-B) to Nakajima A and (KIBAN-C) to Takahashi H
Correspondence to: Hirokazu Takahashi, MD, Gastroenterology Division, Yokohama City University Graduate School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan. hirokazu@med.yokohama-cu.ac.jp
Telephone: +81-45-7872640 Fax: +81-45-7843546
Received: October 13, 2011 Revised: October 20, 2012
Accepted: December 1, 2012
Published online: December 16, 2012

Abstract

AIM: To clarify the relationship of human rectal aberrant crypt foci and formation of colorectal polyp.

METHODS: Eighty-nine subjects were recruited from the population of Japanese individuals who underwent polypectomy at Yokohama City University Hospital. All patients had baseline adenomas removed at year 0 colonoscopy. Aberrant crypt foci (ACF) were defined as lesions in which the crypts were more darkly stained with methylene blue than normal crypts and had larger diameters, often with oval or slit-like lumens and a thicker epithelial lining.

RESULTS: A total of 366 ACFs were identified in 89 patients; all had baseline adenomas removed at the first examination (year 0) colonoscopy and returned for the second (year 1). ACF in the lower rectum were assessed at year 0 and study group were divided into two groups depend on ACF numbers, 0-3 or over 3. All participants were examined in the number and maximum size of adenoma. There was no statistical difference in number and maximum size of ACF at year 0, however, maximum size of adenoma was larger in over 3 group than 0-3 group at year 1.

CONCLUSION: The number of ACF may be a predictive factor of relatively large adenoma incidence in the pilot phase study.

Key words: Aberrant crypt foci; Colorectal carcinogenesis; Visceral fat; Adiponectin

Peer reviewer: Shuhei Yoshida, MD, PhD, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, United State

Takahashi H, Yamada E, Ohkubo H, Sakai E, Higurashi T, Uchiyama T, Hosono K, Endo H, Nakajima A. Relationship of human rectal aberrant crypt foci and formation of colorectal polyp: One-year following up after polypectomy. *World J Gastrointest Endosc* 2012; 4(12): 561-564 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/561.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.561

INTRODUCTION

Colorectal cancer (CRC) has high mortality and morbidity rates, and its prevalence has been increasing[1,2]. The development from normal colonic epithelium to small adenomas is little understood. In experimental models of colonic carcinogenesis, aberrant crypt foci (ACF) are the earliest detectable abnormality and precede adenomas. ACF was first discovered in mice treated with azoxymethane[3], have been clearly shown to be precursor lesions of CRC, and are now established as a biomarker of the risk of CRC in azoxymethane-treated mice and rats[4]. In humans, ACF can be detected using magnifying colonoscopy[5]. Recent advances in magnification chromoendoscopy now allow these lesions to be identified *in vivo* and their natural history ascertained. It would be very useful, to clarify the relationship of ACF incidence to established risks for colorectal tumors. We have reported the relation between number of ACF and visceral fat obesity[6]. In this study, human ACF in the lower rectum were assessed and subjects returned 1 year later to evaluate the natural history of the lesions. Herein, we wanted to determine the adenoma incidence over a 1-year period after polypectomy.

MATERIALS AND METHODS

Study population

We prospectively evaluated 89 subjects recruited from the population of Japanese individuals who underwent polypectomy at Yokohama City University Hospital. All patients had baseline adenomas (over 5 mm) removed at year 0 colonoscopy. The exclusion criteria included: presence of contraindications to colonoscopy; current or past non-steroidal anti-inflammatory drug use including aspirin; or family history of CRC; or history of carcinoma, familial adenomatous polyposis, inflammatory bowel disease, radiation colitis and diabetes mellitus. Written informed consent was obtained from all the subjects prior to their participation. The study protocol was approved by the Yokohama City University Hospital Ethics Committee.

Magnifying colonoscopy for identification of ACF

Participants' bowel preparation for the colonoscopy was carried out using polyethylene glycol solution. A Fujinon EC-490ZW5/M colonoscope was used to perform the magnifying colonoscopy (Fujinon Toshiba ES Systems Co., Ltd, Tokyo, Japan). Total colonoscopy was performed before imaging of lower rectal ACF. Subsequently, 0.25% methylene blue was applied to the mucosa with a spray catheter. Aberrant crypts were distinguished from normal crypts by their deeper staining, larger diameter, must be < 2 mm raised and the number of ACF in the lower rectum was counted. This counting was conducted in the lower rectal region, extending from the middle rectal fold to the dentate line, based on the results of a previous study[5]. ACF were defined as lesions in which the crypts were more darkly stained with methylene blue than normal crypts and had larger diameters, often with oval or slit-like lumens and a thicker epithelial lining[7-10]. All ACF were recorded photographically by one endoscopist and evaluated by two independent observers who were unaware of the subjects' clinical histories.

Measurement of the visceral and subcutaneous fat areas

Body mass index (BMI) was calculated using the following equation: body weight (kg)/[height (m)^2]. Intra-abdominal adipose tissue was assessed, as previously described by measuring the visceral fat area (VFA), subcutaneous fat area (SFA), total fat area (TFA) and waist circumference from computed tomography (CT) images at the level of the umbilicus[6]. All CT scans were carried out with the subjects in the supine position. The borders of the intra-abdominal cavity were outlined on the CT images, and the VFA was quantified using Fat Scan software (N2 System Corporation, Kobe, Japan).

Statistical analysis

We examined the associations between clinical characteristics and number of ACF (0-3 *vs* over 3), because this criteria divided into almost same volume two groups. All data were expressed as mean ± SD, unless otherwise indicated. Non-parametric tests were used to test differences. Statistical analyses were determined using the Stat View software (SAS Institute Inc., Cary, NC, United States). $P < 0.05$ were considered to denote statistical significance.

RESULTS

Patient characteristics

A total of 366 ACFs were identified in 89 patients; all had baseline adenomas (over 5 mm) removed at the first examination (year 0) colonoscopy and returned for the second examination (year 1). ACF in the lower rectum were assessed at year 0 and study group were divided into two groups depend on ACF numbers, 0-3 or over 3. Table 1 summarizes the clinical characteristics of study participants of the first examination. The mean age was 63.4 years and 69% were male. A total of 8% had advanced adenoma, 61% had non advanced adenoma and 31% had no adenoma. There was no statistical difference between 0-3 and over 3 numbers of ACF, in waist circumference, BMI, total cholesterol, triglyceride, hemoglobin A1c, TFA, VFA and SFA.

Natural history of ACF one year follows up after polypectomy

The mean number of observed ACF was 4.1 ± 3.7 at year 0, 4.0 ± 4.6 at year 1. This result shows natural history of ACF, and there was no statistical difference in number of ACF. The typical magnifying colonoscopic features of ACF at year 0 and 1 are shown in Figure 1.

Adenoma incidence and size one year after polypectomy

All participants were assigned two groups, 0-3 or over 3 with number of ACF, and examined in the number and

Table 1 Clinical characteristics of study participants at year 0

	Number of ACF			*P* value
	Total	0-3	> 3	
No. of subjects	89	41	48	
Age (yr)	63.4 ± 11.1	62.6 ± 12.9	64.1 ± 9.5	0.52
Gender (male:female)	61:28:00	28:14:00	33:15:00	
Waist Circumference (cm)	85.9 ± 11.5	84.7 ± 8.1	86.7 ± 13.6	0.57
BMI (kg/m^2)	23.2 ± 3.1	22.6 ± 2.3	23.8 ± 3.6	0.09
Total cholesterol (mg/dL)	210.7 ± 34.9	208.7 ± 32.6	212.2 ± 36.9	0.69
Triglyceride (mg/dL)	146.2 ± 77.1	125.9 ± 64.1	161.5 ± 83.2	0.06
Hemoglobin A1c (%)	5.9 ± 1.3	5.6 ± 1.2	6.2 ± 1.4	0.13
TFA (cm^2)	198.9 ± 95.2	177.0 ± 55.6	215.5 ± 115.2	0.19
VFA (cm^2)	90.4 ± 53.5	75.6 ± 41.1	101.6 ± 59.7	0.11
SFA (cm^2)	108.5 ± 58.1	101.4 ± 45.7	113.9 ± 66.4	0.49

Data are expressed as mean ± SD. ACF: Aberrant crypt foci; BMI: Body mass index; VFA: Visceral fat area; SFA: Subcutaneous fat area; TFA: Total fat area.

Table 2 Endoscopic results of adenoma at year 0 and year 1

No. of aberrant crypt foci at year 0	0-3	> 3	0-3 *vs* > 3
No. of subjects	41	48	
No. of adenoma at year 0	1.4 ± 1.2	1.6 ± 1.8	0.71
Maximum size of adenoma at year 0	6.0 ± 4.6	6.3 ± 7.2	0.81
No. of adenoma at year 1	1.0 ± 1.0	1.5 ± 1.4	0.08
Maximum size of adenoma at year 1	3.5 ± 3.5	5.5 ± 5.8	0.03[1]

Data are expressed as mean ± SD. [1]$P < 0.05$.

maximum size of adenoma (Table 2). There was no statistical difference in number and maximum size of ACF at year 0, however, maximum size of adenoma was larger in over 3 group than 0-3 group at year 1.

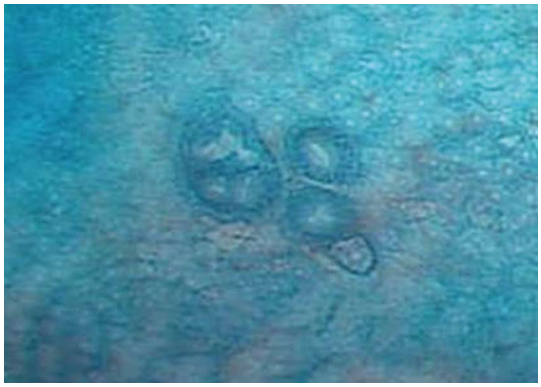

Figure 1 Typical features of aberrant crypt foci on magnifying colonoscopy.

DISCUSSION

Colorectal adenomas are considered to be a validated surrogate endpoint biomarker for sporadic CRC because removing adenomas by endoscopic polypectomy correlates with a decrease in CRC incidence[11]. Therefore, the opportunity of endoscopic polypectomy and needs of predictive colorectal tumor marker are in increasing. ACF have emerged as the putative precursor to colorectal adenomas. In numerous animal studies, ACF predict subsequent development of CRC[12,13]. Cross-sectional studies have shown that there is a higher rate of ACF in subjects with CRC and adenoma compared with those with normal colons[5,14,15]. Because of the epidemiologic and genetic association of ACF with colorectal neoplasia, ACF are a potential biomarker for CRC. Therefore, some chemopreventive studies were reported using ACF as a surrogate marker[16-24]. Natural history of human ACF was reported, however there was no significant change in number of ACF at one year observation[25]. ACF are small lesions and it is possible that the biopsy forceps missed or overwhelmed the lesion. More importantly, because of issues in biopsy orientation and the small number of crypts affected in comparison with the biopsy sample, pathologic diagnosis may not be reliable. Assessment of molecular abnormalities in histologically confirmed ACF and in endoscopically suspected ACF that are not pathologically confirmed will be an additional means of assessing the validity of the endoscopic classification of an ACF. Some studies measuring ACF by magnification chromoendoscopy found a high degree of association between the number of rectal ACF and the presence of synchronous adenomas and adenocarcinomas[26]. In this study, we demonstrated a correlation between the number of ACF 0-3 and over 3 in maximum size of adenoma at year 1. The meaning of the number of ACF is not elucidated, however the number of ACF may be a predictive factor of relatively large adenoma incidence in the pilot phase study.

COMMENTS

Background

Colorectal cancer (CRC) has high mortality and morbidity rates, and its prevalence has been increasing. The development from normal colonic epithelium to small adenomas is little understood. In experimental models of colonic carcinogenesis, aberrant crypt foci (ACF) are the earliest detectable abnormality and precede adenomas. In humans, ACF can be detected using magnifying colonoscopy.

Research frontiers

Recent advances in magnification chromoendoscopy now allow these lesions to be identified *in vivo* and their natural history ascertained. It would be very useful, to clarify the relationship of ACF incidence to established risks for colorectal

tumors.

Innovations and breakthroughs

The authors have reported the relation between number of ACF and visceral fat obesity, however the relation that human ACF and formation of colorectal polyp was unclear.

Applications

In this study, human ACF in the lower rectum were assessed and subjects returned 1 year later to evaluate the natural history of the lesions. Herein, the authors wanted to determine the adenoma incidence over a 1-year period after polypectomy.

Terminology

The meaning of human ACF is still unclear, however may be a surrogate marker of colorectal carcinogenesis. Therefore it is hoped that human ACF will be a surrogate marker of chemopreventive trials.

Peer review

The authors described the relationship of ACF with adenoma. In this study, the authors found maximum size of adenoma was larger in over 3 group than 0-3 group at year 1. It is a novel knowledge and nice to know for gastroenterologist. The authors reviewed their results by relevant high-integrity references. This report is a very interesting study and includes a novel finding. Furthermore, authors described and reviewed well.

REFERENCES

1 **Anderson WF**, Umar A, Brawley OW. Colorectal carcinoma in black and white race. *Cancer Metastasis Rev* 2003; **22**: 67-82
2 **Rougier P**, Mitry E. Epidemiology, treatment and chemoprevention in colorectal cancer. *Ann Oncol* 2003; **14** Suppl 2: ii3-ii5
3 **Bird RP**. Observation and quantification of aberrant crypts in the murine colon treated with a colon carcinogen: preliminary findings. *Cancer Lett* 1987; **37**: 147-151
4 **Pretlow TP**, O'Riordan MA, Somich GA, Amini SB, Pretlow TG. Aberrant crypts correlate with tumor incidence in F344 rats treated with azoxymethane and phytate. *Carcinogenesis* 1992; **13**: 1509-1512
5 **Takayama T**, Katsuki S, Takahashi Y, Ohi M, Nojiri S, Sakamaki S, Kato J, Kogawa K, Miyake H, Niitsu Y. Aberrant crypt foci of the colon as precursors of adenoma and cancer. *N Engl J Med* 1998; **339**: 1277-1284
6 **Takahashi H**, Takayama T, Yoneda K, Endo H, Iida H, Sugiyama M, Fujita K, Yoneda M, Inamori M, Abe Y, Saito S, Wada K, Nakagama H, Nakajima A. Association of visceral fat accumulation and plasma adiponectin with rectal dysplastic aberrant crypt foci in a clinical population. *Cancer Sci* 2009; **100**: 29-32
7 **Roncucci L**, Stamp D, Medline A, Cullen JB, Bruce WR. Identification and quantification of aberrant crypt foci and microadenomas in the human colon. *Hum Pathol* 1991; **22**: 287-294
8 **Roncucci L**, Medline A, Bruce WR. Classification of aberrant crypt foci and microadenomas in human colon. *Cancer Epidemiol Biomarkers Prev* 1991; **1**: 57-60
9 **Pretlow TP**, Barrow BJ, Ashton WS, O'Riordan MA, Pretlow TG, Jurcisek JA, Stellato TA. Aberrant crypts: putative preneoplastic foci in human colonic mucosa. *Cancer Res* 1991; **51**: 1564-1567
10 **Pretlow TP**, O'Riordan MA, Pretlow TG, Stellato TA. Aberrant crypts in human colonic mucosa: putative preneoplastic lesions. *J Cell Biochem Suppl* 1992; **16G**: 55-62
11 **Winawer SJ**, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977-1981
12 **Fenoglio-Preiser CM**, Noffsinger A. Aberrant crypt foci: A review. *Toxicol Pathol* 1999; **27**: 632-642
13 **Corpet DE**, Taché S. Most effective colon cancer chemopreventive agents in rats: a systematic review of aberrant crypt foci and tumor data, ranked by potency. *Nutr Cancer* 2002; **43**: 1-21
14 **Adler DG**, Gostout CJ, Sorbi D, Burgart LJ, Wang L, Harmsen WS. Endoscopic identification and quantification of aberrant crypt foci in the human colon. *Gastrointest Endosc* 2002; **56**: 657-662
15 **Hurlstone DP**, Karajeh M, Sanders DS, Drew SK, Cross SS. Rectal aberrant crypt foci identified using high-magnification-chromoscopic colonoscopy: biomarkers for flat and depressed neoplasia. *Am J Gastroenterol* 2005; **100**: 1283-1289
16 **Hosono K**, Endo H, Takahashi H, Sugiyama M, Sakai E, Uchiyama T, Suzuki K, Iida H, Sakamoto Y, Yoneda K, Koide T, Tokoro C, Abe Y, Inamori M, Nakagama H, Nakajima A. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. *Cancer Prev Res (Phila)* 2010; **3**: 1077-1083
17 **Takahashi H**, Hosono K, Uchiyama T, Sugiyama M, Sakai E, Endo H, Maeda S, Schaefer KL, Nakagama H, Nakajima A. PPARgamma Ligand as a Promising Candidate for Colorectal Cancer Chemoprevention: A Pilot Study. *PPAR Res* 2010; **2010**: pii257835
18 **Sakai E**, Takahashi H, Kato S, Uchiyama T, Hosono K, Endo H, Maeda S, Yoneda M, Taguri M, Nakajima A. Investigation of the prevalence and number of aberrant crypt foci associated with human colorectal neoplasm. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 1918-1924
19 **Anderson JC**, Swede H, Rustagi T, Protiva P, Pleau D, Brenner BM, Rajan TV, Heinen CD, Levine JB, Rosenberg DW. Aberrant crypt foci as predictors of colorectal neoplasia on repeat colonoscopy. *Cancer Causes Control* 2012; **23**: 355-361
20 **Anderson JC**, Pleau DC, Rajan TV, Protiva P, Swede H, Brenner B, Heinen CD, Lambrecht RW, Rosenberg DW. Increased frequency of serrated aberrant crypt foci among smokers. *Am J Gastroenterol* 2010; **105**: 1648-1654
21 **Stevens RG**, Swede H, Heinen CD, Jablonski M, Grupka M, Ross B, Parente M, Tirnauer JS, Giardina C, Rajan TV, Rosenberg DW, Levine J. Aberrant crypt foci in patients with a positive family history of sporadic colorectal cancer. *Cancer Lett* 2007; **248**: 262-268
22 **Mutch MG**, Schoen RE, Fleshman JW, Rall CJ, Dry S, Seligson D, Charabaty A, Chia D, Umar A, Viner J, Hawk E, Pinsky PF. A multicenter study of prevalence and risk factors for aberrant crypt foci. *Clin Gastroenterol Hepatol* 2009; **7**: 568-574
23 **Uchiyama T**, Takahashi H, Endo H, Kato S, Sakai E, Hosono K, Yoneda M, Inamori M, Hippo Y, Nakagama H, Nakajima A. Number of aberrant crypt foci in the rectum is a useful surrogate marker of colorectal adenoma recurrence. *Dig Endosc* 2012; **24**: 353-357
24 **Ohkubo H**, Takahashi H, Yamada E, Sakai E, Higurashi T, Uchiyama T, Hosono K, Endo H, Taguri M, Nakajima A. Natural history of human aberrant crypt foci and correlation with risk factors for colorectal cancer. *Oncol Rep* 2012; **27**: 1475-1480
25 **Schoen RE**, Mutch M, Rall C, Dry SM, Seligson D, Umar A, Pinsky P. The natural history of aberrant crypt foci. *Gastrointest Endosc* 2008; **67**: 1097-1102
26 **Stevens RG**, Swede H, Rosenberg DW. Epidemiology of colonic aberrant crypt foci: review and analysis of existing studies. *Cancer Lett* 2007; **252**: 171-183

S- Editor Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.565

World J Gastrointest Endosc 2012 December 16; 4(12): 565-570
ISSN 1948-5190 (online)

BRIEF ARTICLE

Endoscopy dissection of small stromal tumors emerged from the muscularis propria in the upper gastrointestinal tract: Preliminary study

Zhi-Gang Huang, Xue-Song Zhang, Shi-Liang Huang, Xiao-Gang Yuan

Zhi-Gang Huang, Xue-Song Zhang, Shi-Liang Huang, Xiao-Gang Yuan, Department of Gastroenterology, Lihuili Hospital of Ningbo Medical Center, Ningbo 315040, Zhejiang Province, China

Author contributions: Huang ZG performed all ESD procedures and manuscript writing; Zhang XS assisted during the ESD procedure; Huang SL assisted during the ESD procedure and with data collection; Yuan XG performed the endosonographic evaluation of patients and data collection.

Correspondence to: Dr. Zhi-Gang Huang, Department of Gastroenterology, Lihuili Hospital of Ningbo Medical Center, Ningbo 315040, Zhejiang Province, China. huangzg@foxmail.com

Telephone: +86-574-87018586 Fax: +86-574-87018586
Received: February 26, 2012 Revised: July 4, 2012
Accepted: October 20, 2012
Published online: December 16, 2012

Abstract

AIM: To investigate the feasibility and safety of the treatment of an upper gastrointestinal (GI) submucosal tumor with endoscopic submucosal dissection (ESD).

METHODS: A total of 20 patients with esophageal and gastric submucosal tumors emerged from the muscular layer identified by endoscopic ultrasonography were collected from January 2009 to June 2010. Extramural or dumbbell-like lesions were excluded by an enhanced computerized tomography (CT) scan. All patients had intravenous anesthesia with propofol and then underwent the ESD procedure to resect these submucosal tumors. The incision was closed by clips as much as possible to decrease complications, such as bleeding or perforation, after resection of the tumor. All the specimens were collected and evaluated by hematoxylin, eosin and immunohistochemical staining, with antibodies against CD117, CD34, desmin, α-smooth muscle actin and vimentin to identify the characteristics of the tumors. Fletch's criteria was used to evaluate the risk of gastrointestinal stromal tumors (GISTs). All patients underwent a follow-up endoscopy at 3, 6 and 12 mo and CT scan at 6 and 12 mo.

RESULTS: The study group consisted of 5 men and 15 women aged 45-73 years, with a mean age of 60.2 years. Three tumors were located in the esophagus, 9 in the gastric corpus, 4 in the gastric fundus, 3 lesions in the gastric antrum and 1 in the gastric angulus. Apart from the one case in the gastric angulus which was abandoned due to being deeply located in the serosa, 94.7% (18/19) achieved complete gross dissection by ESD with operation duration of 60.52 ± 30.32 min. The average maximum diameter of tumor was 14.8 ± 7.6 mm, with a range of 6 to 30 mm, and another lesion was ligated by an endoscopic ligator after most of the lesion was dissected. After pathological and immunohistochemical analysis, 12 tumors were identified as a GI stromal tumor and 6 were leiomyoma. Mitotic count of all 12 GIST lesions was fewer than 5 per 50 HPF and all lesions were at very low (9/12, 75.0%) or low risk (3/12, 25.0%) according to Fletch's criteria. Procedure complications mainly included perforation and GI bleeding; perforation occurred in 1 patient and conservative treatment succeeded by a suturing clip and no post-operative GI bleeding occurred. All patients were followed up for 6.5 ± 1.8 mo (range, 3-12 mo) by endoscopy and abdominal CT. Local recurrence and metastasis did not occur in any patient.

CONCLUSION: ESD shows promise as a safe and feasible technique to resect esophageal and gastric submucosal tumors and the incidence of complications was very low. Clinical studies with more subjects and longer follow-up are needed to confirm its treatment value.

Key words: Endoscopic submucosal dissection; Stromal tumors; Leiomyoma; Upper gastrointestinal tract

Peer reviewers: Naoto Sakamoto, Associate Professor, Department of Gastroenterology, Juntendo University, 2-1-1 Hongo Bunkyo-ku Tokyo, Tokyo 113-8421, Japan; Noriya Uedo, Director, Endoscopic Training and Learning Center, Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-0025, Japan

Huang ZG, Zhang XS, Huang SL, Yuan XG. Endoscopy dissection of small stromal tumors emerged from the muscularis propria in the upper gastrointestinal tract: Preliminary study. *World J Gastrointest Endosc* 2012; 4(12): 565-570 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/565.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.565

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common submucosal tumor in the gastrointestinal (GI) tract, accounting for 80% of GI mesenchymal neoplasms, although they are rare, representing only 0.1% to 3% of all GI malignancies[1,2]. It is estimated that there are about 5000 new cases per year in the United States[3]. As more of these lesions are found by virtue of the greater availability of endoscopy, a strategy to manage these lesions will need to be developed.

GISTs show a wide variety of clinical behavior, from benign to frankly malignant, and outcome in individual patients remains difficult to predict[4]. Important parameters of malignancy and prognosis are thought to include tumor size, mitotic index, necrosis, cellularity and proliferative index[5,6]. However, these parameters need *en bloc* specimens and limit their utility in screening and follow-up. To date, total surgical resection still constitutes the only standard treatment for non-metastatic GISTs[7,8] and a wide surgical margin is not necessary for total resection as long as the premise of negative margins is respected in comparison with that of other GI malignant tumors[3].

With more and more submucosal tumors smaller than 2 cm being found, the management of these lesions is a dilemma in clinic practice as they comprise a range of diverse diagnoses (GIST, leiomyoma, ectopic pancreas, neuroendocrine tumor and lipoma)[9]. The diagnosis of a GIST must always be investigated since every GIST is potentially malignant[10,11]. The recent rapid advances in endoscopic intervention therapy provide a potential method for *en bloc* resection of GISTs.

The aim of our study is to investigate the clinical outcomes of endoscopic dissection of small stromal tumors in the upper GI and evaluate the feasibility and safety of endoscopic dissection of the smaller, low risk submucosal stromal tumors.

MATERIALS AND METHODS

Patient characteristics

From January 2009 to June 2010, all 20 patients diagnosed with submucosal tumors emerged from the muscular layer by endoscopic ultrasound (EUS) underwent endoscopic dissection. Extramural or dumbbell-like lesions were excluded by enhanced computerized tomography (CT) scan. Blood routine and prothrombin time were both normal. Nonsteroidal anti-inflammatory drugs such as aspirin and clopidogrel were discontinued on the third preoperative day. All participants signed informed consent before endoscopic dissection.

Endoscopic submucosal dissection procedure

Prior to an endoscopic dissection, all lesions were examined with EUS (GF-UC240P-AL5, Olympus). All patients had intravenous anesthesia with propofol. Endoscopic submucosal dissection (ESD) procedures were performed with the following steps. The margins of the lesion were marked with electrocautery (40W soft coagulation) to determine the resection border. A salt solution containing 0.005 mg/mL epinephrine and 0.1% indigo carmine was injected into the submucosa. After sufficient lifting, a hook knife (KD 620LR, Olympus) was used to create a circumferential incision around the lesion extending into the submucosa. After the circumferential incision, a submucosal dissection with IT knife-2 (KD 611L, Olympus) was made carefully by using the endocut mode of electrosurgical accessories (ICC300; Erbe Co). To avoid bleeding, small vessels were coagulated directly by knives; large vessels with high bleeding risk were coagulated with hemostatic forceps (Olympus). The body of the tumor was gradually exposed and bulged out when the incision was wide enough and the submucosal tumor was snared or continued to be dissected by the IT knife after complete exposure of the root of the tumor. After resection of the tumor, the incision was closed by clips as much as possible to decrease complications, such as bleeding or perforation, and then the specimen was collected with three-claw forceps or a stone basket.

Immunohistochemical analysis

Immunohistochemical staining with antibodies against CD117, CD34, desmin, α-smooth muscle actin (α-SMA) and vimentin was used to identify the tumors. Fletch's criteria[12] was used to evaluate the risk of GISTs.

Definitions and follow-up

All the specimens were evaluated by hematoxylin and eosin stain and immunohistochemistry. Complete gross dissection was defined as the removal of the lesion with the complete capsule, the so-called margin of the lesion was unavailable in the ESD procedure. Patients underwent follow-up endoscopy at 3, 6 and 12 mo and CT scan at 6 and 12 mo.

RESULTS

Patient characteristics

The series consisted of 5 men and 15 women aged 45-73 years, with a mean age of 60.2 years. 19 patients (95%) underwent endoscopy because of epigastric discomfort

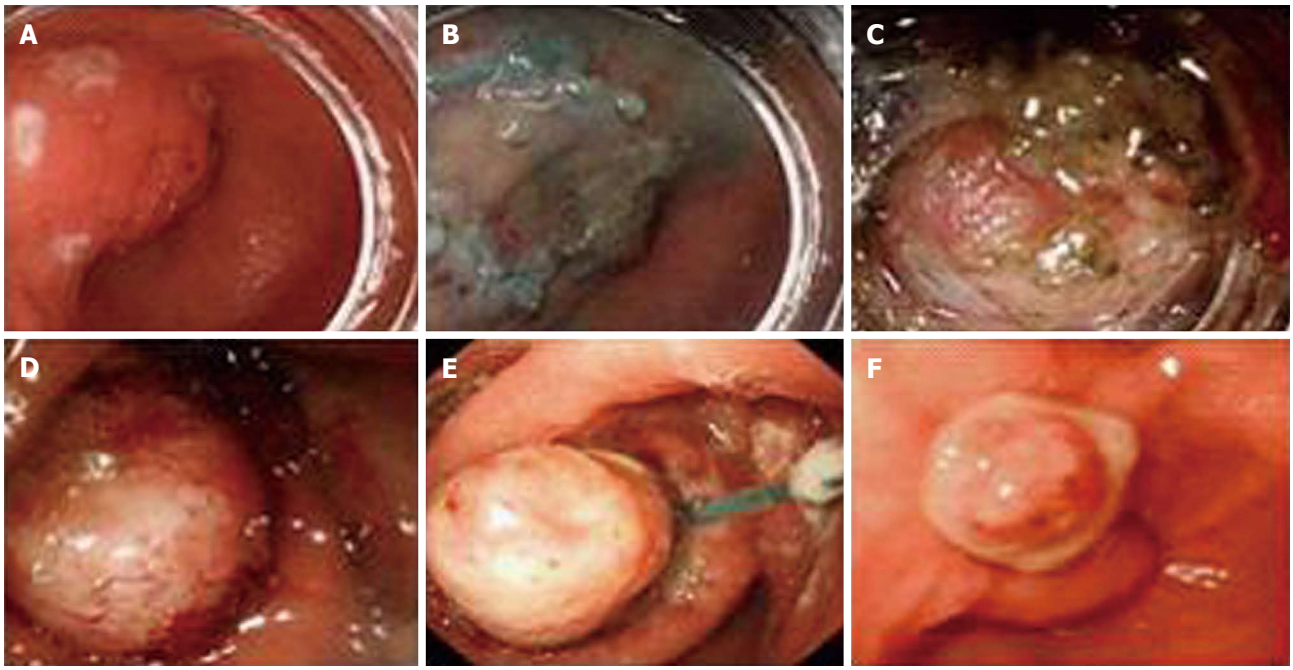

Figure 1 Endoscopic submucosal dissection for submucosal tumor in the antrum. A: Lesion located in the gastric antrum; B: Circumferential incision of the lesion after submucosal injection; C, D: Dissection and exposure of the submucosal lesion; E: Ligation of the root of the lesion with a detachable endoloop; F: Endoscopic follow-up after 1 mo; the lesion disappeared.

or other dyspeptic symptoms and 1 patient with a 3 cm submucosal lesion presented with upper GI bleeding.

Outcomes of endoscopic dissection

Almost all of the patients underwent successful endoscopic dissection, except for one case in the gastric angulus which was abandoned due to being deeply located in serosa. Operation duration was 60.52 ± 30.32 min and the average blood loss was estimated to be less than 50 mL during operation. Furthermore, complete gross dissection was achieved in 94.7% (18/19) of patients without tumor rupture occurring. One lesion located in the antrum, 2.5 × 2.0 cm in size, was ligated by an Olympus HX-20-1 endoscopic ligator with a detachable "endoloop" after most of the lesion was dissected due to conglutination with the muscularis propria and the lesion was found to have completely disappeared in the follow-up after 1 mo (Figure 1). Perforation occurred in one case; the incision was sutured by metal clips (HX-610-090, Olympus), the gastric tube was detained for 3 d and then the patient discharged after 3 d without any complications. All patients were followed up for 6.5 ± 1.8 mo (range, 3-12 mo) by endoscopy and abdominal CT; local recurrence and metastasis did not occur in any patient.

Tumors characteristics and pathological results

Three tumors were located in the esophagus (Figure 2), 9 in the gastric corpus, 4 in the gastric fundus (Figure 3), 3 lesions in the gastric antrum and 1 in the gastric angulus. The average size of tumors was 14.8 ± 7.5 mm, with a range of 6 to 30 mm. Pathological and immunostaining results showed that the 12 submucosal tumors were GISTs and were all located in stomach. 6 lesions were leiomyoma, of which 3 lesions were located in esophagus and the others in the gastric fundus. All the results are shown in Table 1. The mitotic count of 12 GIST lesions was all fewer than 5 per 50 HPF and all lesions were at very low (9/12, 75.0%) or low risk (3/12, 25.0%) according to Fletch's criteria. Among the CD117-positive lesions, CD34 staining was positive in 91.7% (11/12) lesions, vimentin was positive in all lesions and SMA coexisted in 25.0% (3/12) lesions.

DISCUSSION

Generally, all GISTs are considered to be potentially malignant whatever their size, small or large[13,14], and surgery remains the primary treatment for patients with resectable, localized GIST > 2 cm in size. For submucosal tumors smaller than 2 cm in the upper GI tract, the management of these lesions is difficult to handle and the diagnosis of GIST always needs to be identified[15]. Although there are prognostic factors that can stratify GISTs according to their biological behavior, reports exist about the development of metastasis, even in low risk lesions (lesions between 2 cm and 5 cm with fewer than 5 mitoses/50HPF)[16,17], and this means that, if a GIST is suspected, the lesion needs to be resected completely so as to allow risk stratification and reduce the likelihood of metastasis or tumor growth, even when it is small lesion. So, patients with very low or low risk GISTs face two choices: follow-up and bear a heavy psychological burden for a lifetime or undergo surgery. Most patients decline the follow-up option if they know that there is a mini-

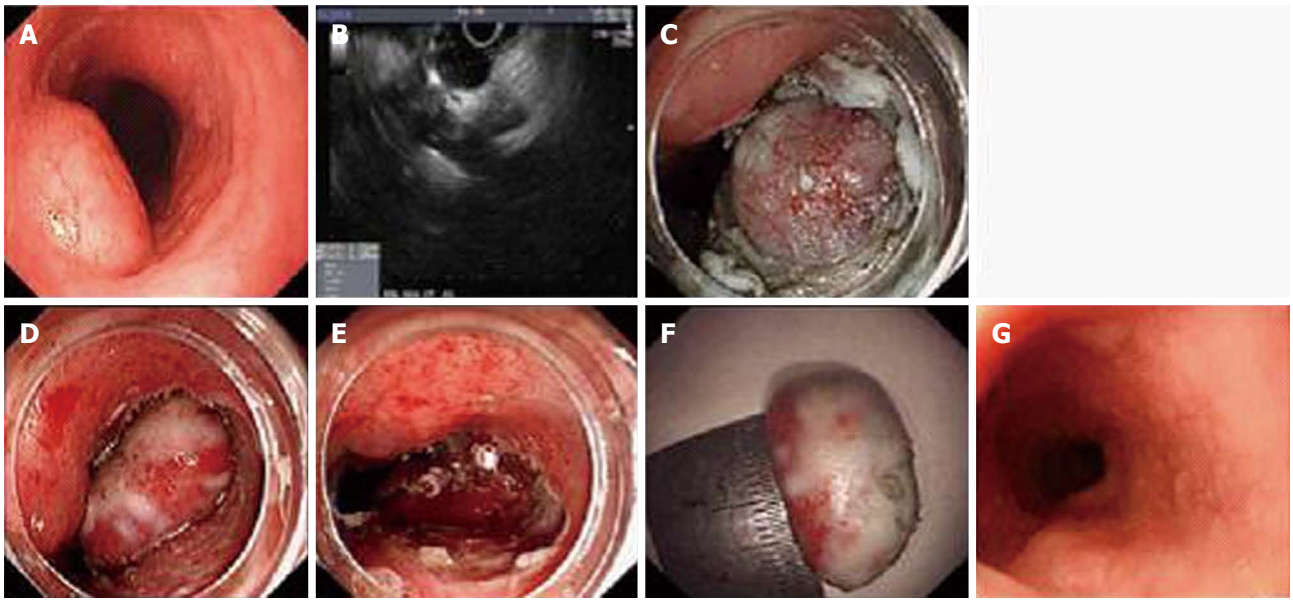

Figure 2 Endoscopic submucosal dissection process for esophageal submucosal tumor. A: Esophageal submucosal tumor located in the median esophagus; B: The lesion was found in the muscularis propria by endoscopic ultrasonography; C, D: The lesion was exposed by dissection of a hook knife and gradually resected by an IT knife-2; E: After the tumor fell off, the cut oozing was stopped using metal clips; F: The lesion (2.0 cm × 1.0 cm) was completely resected with an intact envelope; G: After 2 wk follow-up, the incision disappeared and the wound surface looked smooth.

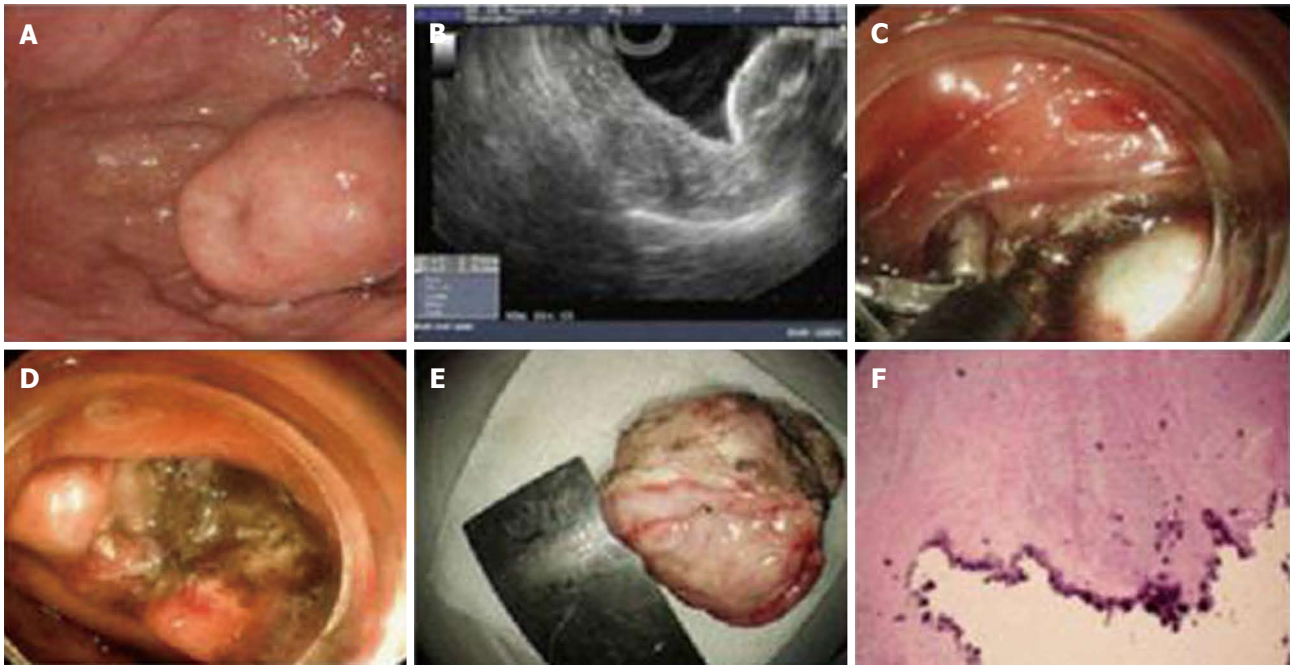

Figure 3 Gastrointestinal stromal tumors in the fundus were dissected by endoscopy. A: Submucosal tumor located in the fundus; B: The lesion was shown in the muscularis propria by endoscopic ultrasonography (EUS); C: White lesion was clearly identified, two clips were used to arrest bleeding from small submucosal vessel; D: The wound surface after dissection of the lesion; E: The dissected tumor (3.0 cm × 2.0 cm) with intact envelope; F: Pathological image of the resected gastrointestinal stromal tumors and calcification in the center of the lesion in accordance with EUS image.

mally invasive technology such as endoscopic resection.

As for the endoscopic approach, endoscopic treatment of GISTs has been little reported for a long time but the role of endoscopy has remained controversial owing to the increased risk of procedure-related complications, such as bleeding, perforation or incomplete resection. The modality of endoscopic treatment includes band ligation[18], polypectomy snare[19] and submucosal dissection[20-23]. The main defect of band ligation is that sloughed specimens are not available for pathological confirmation and risk evaluation and direct polypectomy snare for submucosal tumor face a high risk of perforation and bleeding. In 2010, Bai *et al*[22] reported that submucosal dissection technology for small GISTs < 2

Table 1 Characteristics of submucosal tumors in our case study *n* (%)

Tumor size	
< 1 cm	10 (50)
1-2 cm	6 (30)
2-3 cm	4 (20)
Tumor location	
Esophagus	3 (15)
Stomach	
Fundus	4 (20)
Body	9 (45)
Antrum	3 (15)
Angulus	1 (5)
Pathological results	
Leiomyoma	6 (33)
GIST	12 (67)

GIST: Gastrointestinal stromal tumors.

cm in stomach is feasible with a 28% perforation rate, obviously higher than an overall 4% perforation in ESD for early gastric cancer. Marshall *et al*[24] thought that the high perforation rate in small GISTs dissection cannot be accepted for a very benign condition and the best approach would still be follow-up for small, low risk GISTs unless safer endoscopic technology becomes available. As for full-thickness resection, Zhou *et al*[23] reported the complete resection rate was 100% in 26 patients with a submucosal tumor at a single endoscopy center; no bleeding, peritonitis, abdominal abscess occurred after full-thickness resection and so this technique brought a promising approach to deep, even extramural lesions, but its feasibility needs large scale clinical trials to confirm and resolution of a full-thickness suture technique might be pivotal for its application.

In our case series, the overall removal rate for a submucosal tumor is 95% (19/20) without incidence of serious complications. Sufficiently lifting submucosal tissue around the lesions and prophylactic hemostasis for small vessels are the key technology and blunt dissection by negative pressure suction using a transparent cap is a very helpful skill for facilitating and speeding up the procedure. The difficulty of the procedure is changed by the location of lesions. Lesions located in the fundus, especially adjacent to the cardiac orifice, are much more difficult to resect and the other difficult places include the posterior and lesser curvature in the corpus, the posterior wall of the antrum and the angular notch. To avoid delayed perforation, we selected an endoloop to ligate the lesion after most of lesion was dissected. The main complication (5%, 1/20) is perforation which occurred in only one patient. The incidence of perforation in our series is similar to that of ESD for early gastric cancer. If perforation occurs, endoscopic suture with a clip is the first-line choice and the case of perforation in our study was rehabilitated successfully without surgery. In addition, we suggested that the size of lesions for ESD is better not to exceed 3 cm, as lesions > 3 cm are very difficult to be taken out of the esophageal upper orifice.

In our study, GISTs consisted of 66.7% (12/18) of submucosal lesion confirmed by histopathology; the others were leiomyoma (33.3%, 6/18). Esophageal leiomyoma is the most common benign mesenchymal tumor, accounting for two-thirds of esophageal benign tumors; esophageal leiomyomas less than 5 cm in size generally cause no symptoms[25]. For those larger than 5 cm, surgery or a thoracoscopic operation is always preferentially considered[26,27]. Here, we have successfully resected 3 cases of esophageal leiomyoma emerged from the muscularis propria by endoscopy without any complications, in which the maximum diameter is 2 cm. In fact, most of small esophageal leiomyomas < 1 cm were located in the submucosal layer and we snared directly or resected these lesions by endoscopic mucosal resection (data not shown).

Follow-up in our patients ranged from 3 to 12 mo (mean, 6.5 ± 1.8 mo), during which no recurrence was observed in any patient by endoscopy or EUS. However, judgment of complete resection of GISTs seems to be a little premature because of the limited cases and relatively short follow-up duration. The superiority of endoscopic dissection is *en bloc* removal of entire tumors just like surgical resection but surgery can provide a margin of normal tissue to make a clear pathological diagnosis regarding complete removal of the lesion. Fortunately, a wide margin of normal tissue is not needed in GIST resection, so we can perform endoscopic treatment on GISTs. According to suggested guidelines for accessing malignant potential of GISTs, small GISTs ≤ 3 cm are considered to have a low risk of malignant potential. We recommend that every patient should have close follow-up after endoscopic treatment and it is always beneficial for patients to understand the need for long-term follow-up.

In conclusion, ESD for submucosal tumors shows promise as a relatively safe and feasible technique to treat small submucosal tumors ≤ 3 cm in the upper GI tract. In our pilot study, ESD allowed complete resection of lesions, definitive diagnosis and risk stratification for GISTs without serious procedure-related complications. However, further clinical trials involving many more subjects and a longer period of follow-up are needed.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are the most common submucosal tumors with potential malignancy in the upper gastrointestinal (GI) tract, no matter if their size is small or large, and it is difficult to predict their properties. Total surgical resection remains the mainstay of treatment for non-metastatic GISTs. The recent rapid advances in endoscopic techniques, such as endoscopic submucosal dissection (ESD), provide potential alternative therapeutical methods. However, the feasibility and safety of ESD for GISTs need further clinical evaluation.

Research frontiers

The role of endoscopy for treatment of GISTs has remained controversial because of the risk of procedure-related complications and incomplete resection. However, as a wide negative margin is not needed for GISTs resection, endoscopic management for GISTs is still worth exploring, especially for GISTs no

more than 2 cm.

Innovations and breakthroughs

In the previous studies of ESD for submucosal tumors, a high perforation rate was unacceptable for a relative benign condition and the so-called initiative perforation full-thickness resection for GISTs needed further clinical evaluation unless a safer full-thickness suture was developed. The results showed that ESD for small submucosal tumors in the upper GI tract was a relatively safe and feasible optional treatment besides surgery, but endoscopic ultrasonography should be carried out to evaluate the depth and origin of lesions before endoscopic treatment which would help to avoid unnecessary perforation.

Applications

The results suggest that the ESD technique for small submucosal tumors emerged from submucosal or muscularis propria layer in the upper GI tract is safe and has clinical benefits, such as diagnostic value and a decrease of psychological burden for patients.

Peer review

In this manuscript, the authors described how they obtained the complete resection of submucosal tumors under 3 cm in the upper GI tract and they provide a full account of what is necessary to resect the lesions.

REFERENCES

1 **Nishida T**, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. *Histol Histopathol* 2000; **15**: 1293-1301

2 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001; **438**: 1-12

3 **Chaudhry UI**, DeMatteo RP. Management of resectable gastrointestinal stromal tumor. *Hematol Oncol Clin North Am* 2009; **23**: 79-96, viii

4 **Grotz TE**, Donohue JH. Surveillance strategies for gastrointestinal stromal tumors. *J Surg Oncol* 2011; **104**: 921-927

5 **Liegl-Atzwanger B**, Fletcher JA, Fletcher CD. Gastrointestinal stromal tumors. *Virchows Arch* 2010; **456**: 111-127

6 **Antonescu CR**. Targeted therapy of cancer: new roles for pathologists in identifying GISTs and other sarcomas. *Mod Pathol* 2008; **21** Suppl 2: S31-S36

7 **Gold JS**, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, Maki RG, Singer S, Brennan MF, Antonescu CR, Donohue JH, DeMatteo RP. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol* 2009; **10**: 1045-1052

8 **Gold JS**, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. *Ann Surg* 2006; **244**: 176-184

9 **Gutierrez JC**, De Oliveira LO, Perez EA, Rocha-Lima C, Livingstone AS, Koniaris LG. Optimizing diagnosis, staging, and management of gastrointestinal stromal tumors. *J Am Coll Surg* 2007; **205**: 479-491 (Quiz 524)

10 **Hwang JH**, Kimmey MB. The incidental upper gastrointestinal subepithelial mass. *Gastroenterology* 2004; **126**: 301-307

11 **Rodriguez SA**, Faigel DO. Endoscopic diagnosis of gastrointestinal stromal cell tumors. *Curr Opin Gastroenterol* 2007; **23**: 539-543

12 **Fletcher CD**, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol* 2002; **33**: 459-465

13 **Blay JY**, Bonvalot S, Casali P, Choi H, Debiec-Richter M, Dei Tos AP, Emile JF, Gronchi A, Hogendoorn PC, Joensuu H, Le Cesne A, McClure J, Maurel J, Nupponen N, Ray-Coquard I, Reichardt P, Sciot R, Stroobants S, van Glabbeke M, van Oosterom A, Demetri GD. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20-21 March 2004, under the auspices of ESMO. *Ann Oncol* 2005; **16**: 566-578

14 **Raut CP**, Morgan JA, Ashley SW. Current issues in gastrointestinal stromal tumors: incidence, molecular biology, and contemporary treatment of localized and advanced disease. *Curr Opin Gastroenterol* 2007; **23**: 149-158

15 **Valadão M**, Linhares E. The role of the surgeon in the management of GIST. *Rev Col Bras Cir* 2009; **36**: 261-265

16 **Kim MY**, Park YS, Choi KD, Lee JH, Choi KS, Kim do H, Song HJ, Lee GH, Jung HY, Kim JH, Yun SC, Kim KC, Yook JH, Oh ST, Kim BS, Ryu MH, Kang YK. Predictors of recurrence after resection of small gastric gastrointestinal stromal tumors of 5 cm or less. *J Clin Gastroenterol* 2012; **46**: 130-137

17 **Miettinen M**, El-Rifai W, H L Sobin L, Lasota J. Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review. *Hum Pathol* 2002; **33**: 478-483

18 **Sun S**, Ge N, Wang C, Wang M, Lü Q. Endoscopic band ligation of small gastric stromal tumors and follow-up by endoscopic ultrasonography. *Surg Endosc* 2007; **21**: 574-578

19 **Piccinni G**, Marzullo A, Angrisano A, Iacobone D, Nacchiero M. Endoscopic resection of benign very low-risk gastric gastrointestinal stromal tumors. Is it enough? *Eur J Gastroenterol Hepatol* 2007; **19**: 177-179

20 **Lee IL**, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. *Endoscopy* 2006; **38**: 1024-1028

21 **Hoteya S**, Iizuka T, Kikuchi D, Yahagi N. Endoscopic submucosal dissection for gastric submucosal tumor, endoscopic sub-tumoral dissection. *Dig Endosc* 2009; **21**: 266-269

22 **Bai J**, Wang Y, Guo H, Zhang P, Ling X, Zhao X. Endoscopic resection of small gastrointestinal stromal tumors. *Dig Dis Sci* 2010; **55**: 1950-1954

23 **Zhou PH**, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW, Liu JZ. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surg Endosc* 2011; **25**: 2926-2931

24 **Marshall CA**, Hyatt BJ, Wassef W. Endoscopic removal of small gastrointestinal stromal tumors: can we GIST-ify the risk? *Dig Dis Sci* 2010; **55**: 1815-1817

25 **Punpale A**, Rangole A, Bhambhani N, Karimundackal G, Desai N, de Souza A, Pramesh CS, Jambhekar N, Mistry RC. Leiomyoma of esophagus. *Ann Thorac Cardiovasc Surg* 2007; **13**: 78-81

26 **Choi SH**, Kim YT, Han KN, Ra YJ, Kang CH, Sung SW, Kim JH. Surgical management of the esophageal leiomyoma: lessons from a retrospective review. *Dis Esophagus* 2010; Epub ahead of print

27 **Tay YC**, Ng CT, Lomanto D, Ti TK. Leiomyoma of the oesophagus managed by thoracoscopic enucleation. *Singapore Med J* 2006; **47**: 901-903

S- Editor Song XX **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.571

World J Gastrointest Endosc 2012 December 16; 4(12): 571-574
ISSN 1948-5190 (online)

CASE REPORT

Case of obscure-overt gastrointestinal bleeding after pediatric liver transplantation explained by endoscopic ultrasound

Gabriele Curcio, Marta Di Pisa, Roberto Miraglia, Pieralba Catalano, Luca Barresi, Ilaria Tarantino, Antonino Granata, Marco Spada, Mario Traina

Gabriele Curcio, Marta Di Pisa, Luca Barresi, Ilaria Tarantino, Antonino Granata, Mario Traina, Department of Gastroenterology, Liver Transplantation Unit, IsMeTT, 90100 Palermo, Italy
Roberto Miraglia, Department of Radiology, Liver Transplantation Unit, IsMeTT, 90100 Palermo, Italy
Pieralba Catalano, Marco Spada, Department of Pediatric, Liver Transplantation Unit, IsMeTT, 90100 Palermo, Italy
Author contributions: Curcio G was the lead investigator; Curcio G, Miraglia R and Catalano P performed the research; Granata A contributed new analytic tools; Curcio G, Barresi L, Tarantino I and Spada M analyzed the data; Curcio G and Di Pisa M wrote the paper; Traina M gave final approval.
Correspondence to: Gabriele Curcio, MD, Department of Gastroenterology, Liver Transplantation Unit, IsMeTT, UPMC, Via Tricomi 1, 90100 Palermo, Italy. gcurcio@ismett.edu
Telephone: +39-91-2192111 Fax: +39-91-2192400
Received: June 22, 2011 Revised: November 7, 2011
Accepted: April 27, 2012
Published online: December 16, 2012

Abstract

Portal hypertension, which is a common finding in children awaiting liver transplantation, is also found after transplantation. It's reported the case of a 6-year-old girl, transplanted for biliary atresia, who had a severe obscure-overt bleeding presenting with melena. An esophagogastroduodenoscopy showed several duodenal small, bulging lesions, with some red signs. Near the lesions, a depressed area of 2 cm, covered with mixed hyperemic and white mucosa, was observed. To better evaluate these lesions, we performed an endoscopic ultrasonography (EUS) that showed multiple, round hypoechoic areas 0.5-5 mm in diameter, compatible with duodenal varices, and several periduodenal anechoic lesions compatible with collaterals. A consecutive computed tomography scan showed a stenosis of the portal vein anastomosis confirmed with a transhepatic portography, which was successfully treated with balloon angioplasty. No further episodes of bleeding were observed during the follow-up. This case report suggests that EUS is safe and feasible in young children when using echoendoscopes designed for use in adults. However further studies are needed to validate the employment of this technique in the management and follow-up of pediatric portal hypertension.

Key words: Obscure bleeding; Pediatric; Endoscopic ultrasound; Liver transplantation; Gastrointestinal

Peer reviewer: John A Karagiannis, Professor, Department of Gastroenterology, Konstantopoulio Hospital, 6, Iordanidi Str. P. Psychiko, 15452 Athens, Greece

Curcio G, Di Pisa M, Miraglia R, Catalano P, Barresi L, Tarantino I, Granata A, Spada M, Traina M. Case of obscure-overt gastrointestinal bleeding after pediatric liver transplantation explained by endoscopic ultrasound. *World J Gastrointest Endosc* 2012; 4(12): 571-574 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/571.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.571

INTRODUCTION

Biliary atresia (BA) is a common cause of neonatal cholestasis, with an approximate incidence of 1:10 000-15 000 live births[1]. Liver transplantation (LT) has become an important option for providing excellent long-term survival for patients with BA[2]. However, after LT, vascular[3] and biliary complications[4,5] can occur, and these are associated with increased morbidity and mortality.

Portal hypertension (PH)[6], which is a common finding in children awaiting liver transplantation, is also found after transplantation[7]. A diagnosis of PH can routinely be made by upper gastrointestinal endoscopy. Moreover, in recent years, endoscopic ultrasonography (EUS) has become a complementary modality for the diagnosis and treatment of this condition.

Very little data on PH in infants are available, especially for routine EUS applications in these young patients[8].

We report the case of a 6-year-old girl, transplanted for BA, who had a severe obscure-overt bleeding, in which EUS allowed us to diagnosis severe portal hypertension, with ectopic varices, and to plan the successive diagnostic steps and the adequate treatment.

CASE REPORT

In June 2010, a 6-year-old girl was admitted to our institute because of an episode of melena with severe anemia. She had been affected with BA at the age of 1 mo. Although she underwent a Kasai procedure at the age of 2 mo, she developed cirrhosis, and at 8 mo underwent a cadaveric liver transplant, using an ABO-compatible, split-liver graft (segment Ⅱ-Ⅲ). The post transplant clinical course was complicated by an episode of acute rejection, successfully treated with steroids. An anastomotic biliary stricture occurred in February 2010. It was successfully treated with percutaneous biliary catheter placement, and subsequent sessions of cholangioplasty. The patient had been free of the biliary catheter since June 2010. Doppler ultrasound (US) performed at follow-up found no abnormalities in the hepatic artery, hepatic veins or portal vein. No other adverse events occurred until her episode of melena. On admission, she was in stable general condition, and asymptomatic. Her physical examination was unremarkable, with an arterial pressure of 110/60 mmHg. Laboratory data showed hemoglobin 6 gr/dL (NV: 12-16 gr/dL); PLT 193.000 $\times 10^3/\mu L$ (150-400 $\times 10^3/\mu L$); MCV 76.70 (78-102 fL); total bilirubin 0.31 (0.10-1.10 mg/dL); direct bilirubin 0.11 (0-0.30 mg/dL); aspartate aminotransferase 133 (15-37 U/L); alanine aminotransaminase 203 (30-65 U/L); alkaline phosphatase 362 (50-136 U/L); and glutamyltransferase 48 (5-85 U/L). Two units of blood were transfused and, in order to check the cause of the anthemization, an esophagogastroduodenoscopy (EGD) was planned. Under deep sedation, the patient was monitored continuously with electrocardiography, pulse oximetry and automatic recording of blood pressure and pulse. After introducing the scope into the esophagus, small varices, with no red signs, were seen in the lower third. The stomach was normal. There were no signs of active bleeding. In the duodenum, at the bulb apex, several small, bulging lesions, with some red signs, were seen. Near the lesions, a depressed area of 2 cm, covered with mixed hyperemic and white mucosa, was observed (Figure 1A). To evaluate the nature of these lesions, and using the same sedation, a 20 MHz miniprobe (Olympus Medical System Corp.) was inserted into the operative channel of the endoscope. After filling the duodenal lumen with water, multiple, round hypoechoic areas 0.5-5 mm in diameter, compatible with varices, were seen in correspondence to the endoscopically viewed lesions (Figure 1B).

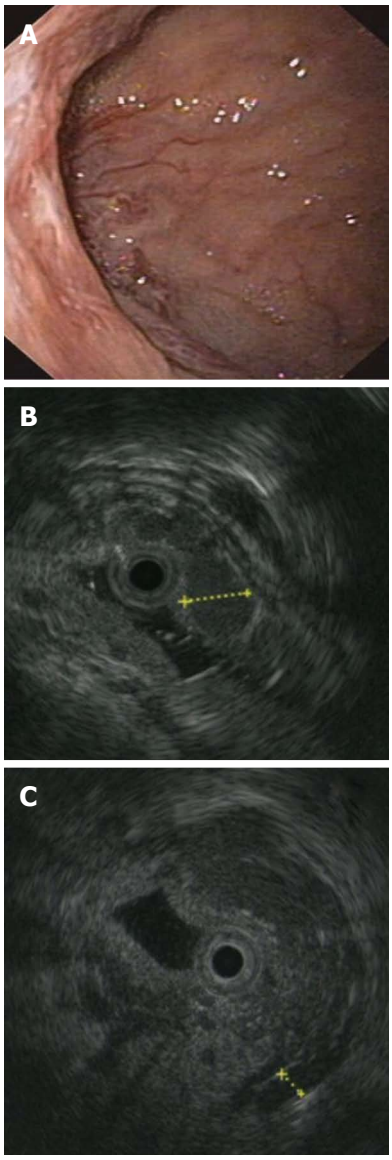

Figure 1 Lesions in the duodenum. A: Depressed area of 2 cm, covered with mixed hyperemic and white mucosa, seen at EGDS; B: Round hypo-anechoic areas of 5 mm in diameter, compatible with vascular structures (varices), in the duodenal mucosa; C: Periduodenal anechoic lesions compatible with collaterals.

In addition, the EUS showed several periduodenal anechoic lesions (Figure 1C), compatible with collaterals, and confirmed small varices in the esophagus. Because the EUS showed a picture of portal hypertension with ectopic duodenal varices, despite the normal Doppler US findings, a computed tomography scan was done, and showed a stenosis of the portal vein anastomosis. The false-negative finding of the Doppler US was likely related to the deep position of the anastomosis, which

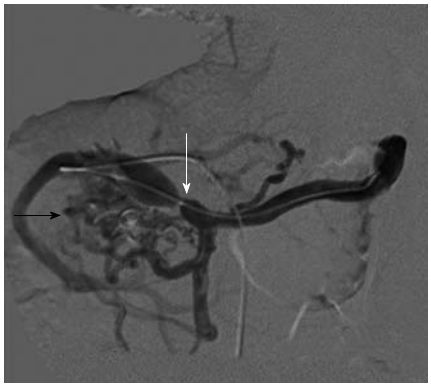

Figure 2 Transhepatic portography showing a severe anastomotic stenosis (arrow), and filling of multiple periduodenal varices (arrow head).

was covered by bowel loops. A transhepatic portography was done the day after, showing multiple periduodenal varices and confirming the anastomotic stricture, which was successfully treated with balloon angioplasty (Figure 2). Over the following days, the patient remained hemodynamically stable, with no further episodes of bleeding. Two weeks later, at EGD and EUS control, no duodenal varices were found (Figure 3A and B).

DISCUSSION

Endoscopic ultrasonography has recently emerged as an accurate, non-invasive and reproducible technique, and is more sensitive than endoscopy in the diagnosis of gastric varices[9]. Dilated venous abnormalities outside the gastroesophageal lumen, which cannot be diagnosed by endoscopy, are readily visible with endoscopic ultrasonography or miniature probes. However, this method has yet to become a routine examination among the diagnostic and therapeutic examinations in the setting of portal hypertension[10]. As for the application of EUS in pediatric patients[11], several reports have been published, though with few indications regarding the use of radial endoscopic probes in pancreatobiliary disorders, gastrointestinal tumors and portal hypertension[12]. As a result, there are few data on the use of ultrasonographic miniprobes for studying vascular abnormalities in pediatric portal hypertension. In our case, the patient developed varices 4 years after liver transplant, and we were able to confirm the presence of ectopic duodenal varices, which can account for up to 5% of variceal hemorrhages[8]. We used a 20 MHz miniprobe, which was introduced into the operative channel of the endoscope. The ultrasonography procedure with miniprobes is safe, non-invasive and does not require preparation. In addition, we can do both gastroscopy and endoscopic ultrasonography using the same sedation and without changing the instrument. The easiness and the quickness of this combined approach allowed us to identify severe portal hypertension despite the endoscopic appearance, and also to plan the successive diagnostic and therapeutic steps. Unfortunately, despite the advantages of EUS, its use in pediatric patients

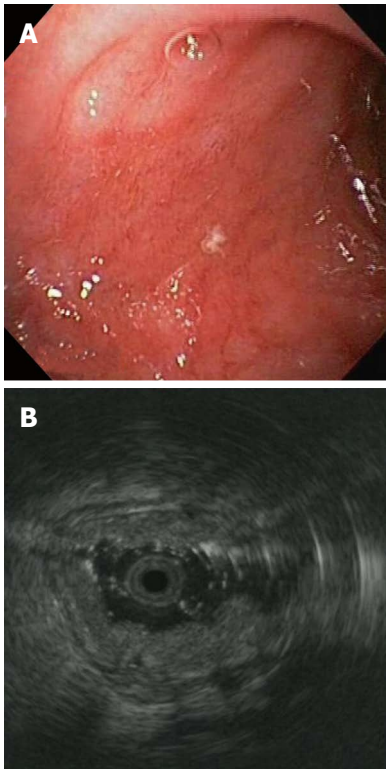

Figure 3 Normal endoscopic appearance of the bulb (A) and normal stratification of the duodenal layers (B).

is very limited because of the presumptive limitations inherent in the size of EUS equipment and accessories, the need for an anesthesiologist in the endoscopic room, and the lack of highly trained and experienced endosonographers for pediatric patients[13]. This case report suggests that EUS is safe and feasible in young children when using echoendoscopes designed for use in adults. Further studies are needed to validate the employment of this technique in the management and follow-up of pediatric portal hypertension.

ACKNOWLEDGMENTS

We thank Warren Blumberg for editorial assistance.

REFERENCES

1 **Bassett MD**, Murray KF. Biliary atresia: recent progress. *J Clin Gastroenterol* 2008; **42**: 720-729
2 **Zheng SS**, Huang DS, Wang WL, Liang TB, Zhang M, Shen Y, Lu AW, Liao SY, Xu X. Living related liver transplantation for an infant with biliary atresia. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 172-175
3 **Pareja E**, Cortes M, Navarro R, Sanjuan F, López R, Mir J. Vascular complications after orthotopic liver transplantation: hepatic artery thrombosis. *Transplant Proc* 2010; **42**: 2970-2972
4 **Egawa H**, Uemoto S, Inomata Y, Shapiro AM, Asonuma K, Kiuchi T, Okajima H, Itou K, Tanaka K. Biliary complications in pediatric living related liver transplantation. *Surgery* 1998; **124**: 901-910
5 **Chen HL**, Concejero AM, Huang TL, Chen TY, Tsang LL, Wang CC, Wang SH, Chen CL, Cheng YF. Diagnosis and interventional radiological treatment of vascular and biliary

complications after liver transplantation in children with biliary atresia. *Transplant Proc* 2008; **40**: 2534-2536
6 **Mileti E**, Rosenthal P. Management of portal hypertension in children. *Curr Gastroenterol Rep* 2011; **13**: 10-16
7 **Chu J**, Kerkar N, Miloh TA, Rodriguez-Laiz G, Lewis B, Stangl A, Newton KP, Iyer K, Arnon R. Roux-en-Y loop varices in children with portal hypertension after liver transplantation: an unusual cause of "obscure" gastrointestinal bleeding. *Pediatr Transplant* 2011; **15**: E156-E161
8 **Norton ID**, Andrews JC, Kamath PS. Management of ectopic varices. *Hepatology* 1998; **28**: 1154-1158
9 **El-Saadany M**, Jalil S, Irisawa A, Shibukawa G, Ohira H, Bhutani MS. EUS for portal hypertension: a comprehensive and critical appraisal of clinical and experimental indications. *Endoscopy* 2008; **40**: 690-696
10 **Bocus P**, Ceolin M, Battaglia G. Endoscopic ultrasonography (EUS) in portal hypertension. *Minerva Med* 2007; **98**: 431-436
11 **Cohen S**, Kalinin M, Yaron A, Givony S, Reif S, Santo E. Endoscopic ultrasonography in pediatric patients with gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2008; **46**: 551-554
12 **Varadarajulu S**, Wilcox CM, Eloubeidi MA. Impact of EUS in the evaluation of pancreaticobiliary disorders in children. *Gastrointest Endosc* 2005; **62**: 239-244
13 **Attila T**, Adler DG, Hilden K, Faigel DO. EUS in pediatric patients. *Gastrointest Endosc* 2009; **70**: 892-898

S- Editor Yang XC **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i12.575

World J Gastrointest Endosc 2012 December 16; 4(12): 575-578
ISSN 1948-5190 (online)

CASE REPORT

First Pillcam Colon 2 capsule images of Whipple's disease: Case report and review of the literature

Bogdan Radu Mateescu, Andreea Bengus, Madalina Marinescu, Florica Staniceanu, Gianina Micu, Lucian Negreanu

Bogdan Radu Mateescu, Andreea Bengus, Madalina Marinescu, Department of Gastroenterology, Colentina Hospital, Bucharest 50098, Romania
Florica Staniceanu, Gianina Micu, Department of Pathology, Colentina Hospital, Bucharest 50098, Romania
Lucian Negreanu, Department of Internal Medicine 2-Gastroenterology, University Hospital, Bucharest 50098, Romania
Author contributions: Mateescu BR, Bengus A and Negreanu L wrote the manuscript; Negreanu L and Marinescu M revised the capsule readings; Staniceanu F and Micu G realized the pathology exams; Negreanu L made the final corrections and wrote the manuscript.
Supported by ESGE-Given research grant 2010
Correspondence to: Lucian Negreanu, MD, PhD, Assistant Professor, Head of Internal Medicine 2 Department, Department of Internal Medicine 2-Gastroenterology, University Hospital, Splaiul Independentei 169, sector 5, Bucharest 50098, Romania. negreanu_99@yahoo.com
Telephone: +40-72-2546405 Fax: +40-21-3180505
Received: September 7, 2011 Revised: March 4, 2012
Accepted: October 10, 2012
Published online: December 16, 2012

Abstract

Whipple's disease is a rare chronic systemic infection determined by the Gram-positive bacillus *Tropheryma whipplei*. The infection usually mainly involves the small bowel, but sometimes other organs are affected as well. Since the current standard clinical and biological tests are nonspecific, diagnosis is very difficult and relies on histopathology. Here we present the case of a 52-year-old man with chronic diarrhea and weight loss whose symptoms had been evolving for 2 years and whose diagnosis came unexpectedly after capsule examination. Diagnosis was confirmed by the histopathologic examination of endoscopic biopsy samples, and treatment with co-trimoxazole resulted in remission of symptoms. We present the first images of Whipple's disease obtained with the Pillcam Colon 2 video capsule system.

Key words: Whipple's disease; Malabsorption; Capsule endoscopy; Pillcam Colon 2

Peer reviewer: Omar Javed Shah, Professor, Head, Department of Surgical Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar 110029, Kashmir, India

Mateescu BR, Bengus A, Marinescu M, Staniceanu F, Micu G, Negreanu L. First Pillcam Colon 2 capsule images of Whipple's disease: Case report and review of the literature. *World J Gastrointest Endosc* 2012; 4(12): 575-578 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i12/575.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i12.575

INTRODUCTION

Whipple's disease is a rare chronic systemic infection determined by the Gram-positive bacillus *Tropheryma whipplei*. The infection usually mainly involves the small bowel, but sometimes other organs are affected as well. Since the current standard clinical and biological tests are nonspecific, diagnosis is very difficult and relies on histopathology.

CASE REPORT

A 52-year-old man presented in our department with chronic diarrhea: 6-10 watery stools/d without mucus or blood, low fever (37-38 ℃), and progressive asthenia. Stools were exclusively diurnal, described as "sticky", with no visible blood.

Symptoms started 2 years before, but since then the patient had lost 15 kg, despite his appetite being preserved. He denied drinking alcohol or smoking and didn't have a significant personal or familial medical history. The patient was repeatedly evaluated in infectious diseases departments, but all the stool cultures (*Shigella*, *Salmonella*, enteropathogenic or enterotoxigenic *Escherichia coli*, and *Campylobacter jejuni*) were negative. Since the stools were

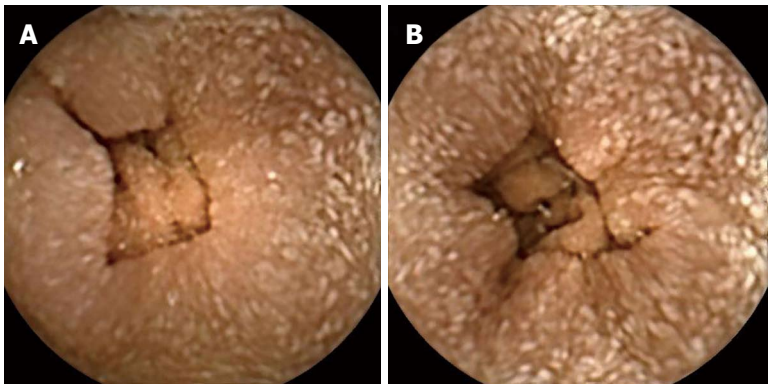

Figure 1 Video capsule examination showing small, white, diffuse deposits, covering all the small bowel mucosa (A and B). The villi are present and edematous.

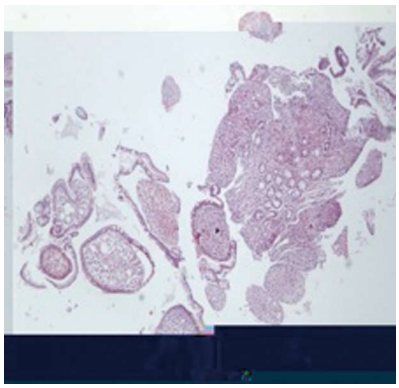

Figure 2 Whipple's disease, small intestine with flattened villi, expanded by a dense infiltrate of foamy macrophages (hematoxylin and eosin, 4 x). Mall bowel mucosa; the villi are present and edematous.

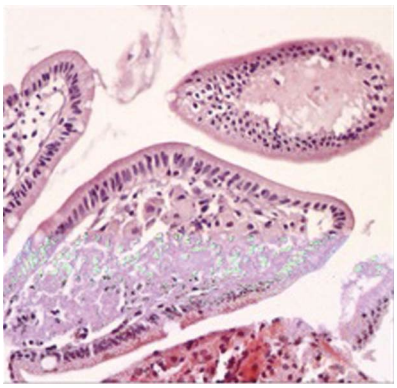

Figure 3 Whipple' disease-small intestine with polymorphonuclear and foamy macrophages (hematoxylin and eosin, 20 x).

found several times to be positive for *Giardia lamblia*, the patient underwent several rounds of metronidazole, but to no clinical improvement. Hyperthyroidism and celiac disease were excluded. Multiple gastroscopies found no lesions, except some diffuse white small deposits in D2 (but no anomalies on histopathology). The patient underwent 3 subtotal colonoscopies, which were described as normal.

In addition to antiparasitic drugs, he received antidiarrheals and spasmolytics, with partial, albeit temporary, symptom alleviation. Clinical examination showed the patient to be in a poor state: he was pale, underweight (body mass index 20.1), had a body temperature of 37.5 ℃, and suffered diffuse pain and increased bowel sounds at abdominal palpation; discrete peripheral edema, and pulmonary and cardiovascular examinations were normal. No enlarged lymph nodes, skin lesions, or signs of articular involvement were noticed.

The only laboratory anomalies found at this time were a mild hyposideremic anemia (hemoglobin 9.12 g/dL, hematocrit 29%, serum iron 10 μg/dL), with hypoalbuminemia (2.9 g/dL), and an inflammatory syndrome [(C-reactive protein (CRP) 84.7 mg/L], suggesting a lesion of the absorptive epithelium.

Because the patient refused a new colonoscopy, we used the new Pillcam Colon 2 video capsule from given imaging. There were no anomalies in the esophagus, stomach, or first part of the duodenum, but a "salt and pepper" aspect of the entire small bowel, ending at the ileocecal valve, was noticed. This aspect was due to a myriad of 1-2 mm white deposits (suggesting small intraepithelial abscesses) covering the mucosa (Figure 1). An upper endoscopy and ileocolonoscopy were performed, and multiple biopsies were taken from the small bowel mucosa.

In the pathology lab, after paraffin embedding, the tissue samples were sectioned in 3 μm slices. The slides were then stained with hematoxylin and eosin (HE) and Periodic Acid Schiff (PAS). The HE stain showed: small intestinal mucosa with flattened villi, expanded by a dense infiltrate of foamy macrophages with finely granular eosinophilic cytoplasm, and moderate neutrophilic infiltrate in the lamina propria (Figures 2, 3 and 4). PAS coloration: showed foamy macrophages with frequent PAS-positive bacilli in the cytoplasm, which was suggestive for *Tropheryma whipplei* (Figure 5).

Given the lack of signs of neurologic involvement, we started oral co-trimoxazole (800/160 mg/d). Ten days later, the patient's general condition improved, with an increase in appetite, and a slight reduction in bowel movements (4-5/d) and in CRP (51 mg/L). The patient was re-examined every 2 wk. His appetite continued to increase and, by the end of the second month of therapy, he had gained 7 kg in weight. The number of stools decreased to 2-3/d, the CRP fell to 19 mg/dL and his

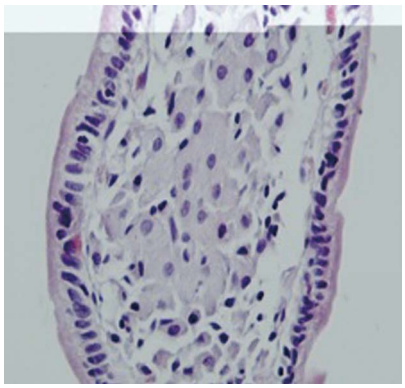

Figure 4 Whipple's disease-intestinal villi with foamy macrophages (hematoxylin and eosin, 40 x).

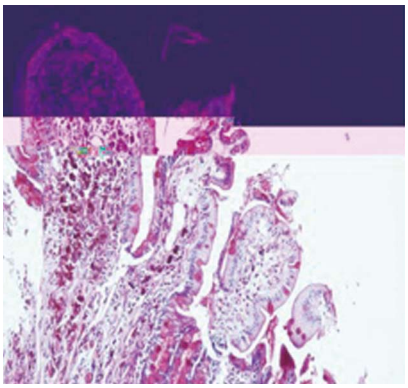

Figure 5 Whipple's disease-foamy macrophages with Periodic Acid Schiff positive bacilli in the cytoplasm (10 x).

temperature returned to normal; we chose not to administer martial therapy for fear of an iron-induced change in bowel transit, and to allow a spontaneous increase in hemoglobin as a sign of recovering intestinal absorptive functions; indeed there was a 1.1 g/dL increase in hemoglobin at 2 mo. We plan to continue the same treatment and to recheck the endoscopic aspect in 6 mo.

DISCUSSION

Whipple described for the first time[1] in 1907 this chronic, systemic infection, caused by a Gram-positive bacillus. Although the existence of an infectious organism was postulated by Whipple himself, it took 85 years to completely characterize the bacteria by amplification of the genetic material[2], and another 5 years to isolate it[3]. It was named *Tropheryma whipplei* (*T. whippelii*) and included in the same order (*Actinomycetales*) as the Actinomyces genus. The analysis of its genome and the lack of some essential biosynthetic equipment[4] suggest an intracellular parasite.

Whipple's disease is very rare; according to a recent review[5], only about 1000 cases have been documented worldwide, mostly in middle-age Caucasian farmers or in those working with soil. The bacillus is present in sewage water and in the soil[6], and the majority of infected humans are healthy carriers who do not develop the disease, pointing toward an underlying genetic predisposition. A particular human leukocyte antigen profile and defects in the cell-mediated immune response predispose to the classical form of the disease, manifesting as diarrhea, malabsorption, weight loss, arthritis or arthralgia, fever, lymphadenopathy, abdominal pain, and neurological signs. The central nervous system (CNS) involvement is the most serious manifestation of the disease, and occurs in up to 43% of cases[7]: headache, cognitive dysfunctions, and disturbances of the ocular movement, in particular progressive supranuclear ophthalmoplegia in conjunction with oculomasticatory myorhythmia, which are considered pathognomonic[8]. Rarely, focal signs may be present or the CNS[9] or joint involvement may be the sole sign of disease. Recently, other clinical entities caused by this bacterium have been recognized; acute self-limited diarrhea or the isolated endocarditis.

The rarity of the disease and the lack of specificity of the clinico-biologic picture make diagnosis very difficult. Confirmation is obtained by finding PAS-positive material (phagocytized bacilli) inside the macrophages from mucosal biopsies by immunohistochemistry, by the identification of *T. whipplei* in electronic microscopy or through the identification of bacterial DNA with polymerase chain reaction; all tests have a similar sensitivity. We are awaiting novel diagnostic methods; serologic diagnosis is hampered by the reduced reactivity in patients with Whipple's disease compared with asymptomatic carriers[10].

Colon capsule endoscopy (CCE) represents a noninvasive technology that allows visualization of the colon without requiring sedation and air insufflation. CCE may be a means to overcome the low adherence to colonoscopy in colorectal cancer screening[11].

A second-generation CCE system (PillCam Colon 2; CCE-2) was developed to increase sensitivity for colorectal polyp detection compared with the first-generation system. The PillCam Colon 2 (31 mm × 11 mm) has some new features: the angle of view has been widened from 154° to 172° for each camera, thus offering a panoramic view, and the data recorder was revolutionized (it recognize the location of the capsule and its speed, and permits an adaptive frame rate of 4-35 images/s). The rapid software was upgraded substantially.

In a French study on 128 patients, CCE seemed to be effective in detecting clinically significant colonic findings in patients with an indication of colonoscopy with a high negative predictive value and an excellent tolerance[12].

The results were confirmed in a European multicenter study where CCE-2 appeared to have a high sensitivity for the detection of clinically relevant polypoid lesions. The authors concluded that CCE might be considered an adequate tool for colorectal imaging[13].

In 2010 our team won the ESGE given grant at the United European Gastroenterology Week, with a project on the use of Pillcam Colon 2 for the patients at risk of colorectal cancer (CRC) unwilling or unable to perform colonoscopy[14].

Our patient had three incomplete colonoscopies in other units before, with failures due to technical difficul-

ties and low tolerance of the examination. He refused any new endoscopic examinations, but when we decided to propose the use of Pillcam Colon 2 the patient agreed. The aspect of 1-2 mm white deposits (suggesting small intraepithelial abscesses) covering the mucosa confirmed our suspicion of a small bowel disease, and convinced the patient to perform the more "aggressive" investigations, and thus allowed the biopsies and the histologic confirmation of Whipple's disease. This is a fine example of the increasing compliance to an examination using CCE. It acceptability is growing globally, not only in CRC screening, but also in many uncommon diseases, as it is patient-friendly. Its use in the pediatric population is well accepted. Previous descriptions of Whipple's disease using SB were made by different team's capsules[15,16]. Capsule endoscopy was also used as a monitoring tool to observe mucosal healing after antibiotic therapy[17], but this is the first description, to our knowledge, of Whipple's disease using the new Pillcam Colon 2 video capsule system.

Before the antibiotic era, Whipple's disease was always lethal, most frequently due to severe malabsorption. Tetracycline, a preferred drug, like many other antibiotics active against *T. whipplei*, does not cross the blood-brain barrier, and was associated with a high rate of relapse inside the central nervous system; that is why today it is recommended to use an antibiotic with good penetration into the brain (e.g., co-trimoxazole; in fact only the sulfamethoxazole component is active). A recent randomized trial[18] found the superiority of an induction treatment with intravenous ceftriaxone or meropenem associated with oral co-trimoxazole for 12 mo over the classical 12 mo of oral co-trimoxazole alone. Oral therapy alone has been advocated for those cases without proof of neurologic involvement[19]. However, other trials searching for the best regimen are in progress. Recovery is usually complete, but sometimes the neurologic lesions are irreversible. Relapses should be treated with an alternative regimen, always including antibiotics with good penetration into the brain (e.g., penicillin G, chloramphenicol, and carbapenems). Proof of cure is based on clinical grounds (usually the diarrhea and malabsorption improve in weeks), with polymerase chain reaction (which is quickly negated after efficient therapy), and on repeat endoscopy with biopsies (with the endoscopic changes disappearing in weeks, although the histological aspect may persist for several years[18]).

In conclusion, Whipple's disease is a rare bacterial infectious disease affecting the gasterointestinal tract which has previously been diagnosed by capsule endoscopy. This may be the first published report with Pillcam Colon 2, which is a new and exciting noninvasive diagnostic technique.

REFERENCES

1 **Whipple GH**. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull Johns Hopkins Hosp* 1907; **18**: 382-391

2 **Relman DA**, Schmidt TM, MacDermott RP, Falkow S. Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med* 1992; **327**: 293-301

3 **Raoult D**, Birg ML, La Scola B, Fournier PE, Enea M, Lepidi H, Roux V, Piette JC, Vandenesch F, Vital-Durand D, Marrie TJ. Cultivation of the bacillus of Whipple's disease. *N Engl J Med* 2000; **342**: 620-625

4 **Raoult D**, Ogata H, Audic S, Robert C, Suhre K, Drancourt M, Claverie JM. Tropheryma whipplei Twist: a human pathogenic Actinobacteria with a reduced genome. *Genome Res* 2003; **13**: 1800-1809

5 **Fenollar F**, Puéchal X, Raoult D. Whipple's disease. *N Engl J Med* 2007; **356**: 55-66

6 **Fenollar F**, Trani M, Davoust B, Salle B, Birg ML, Rolain JM, Raoult D. Prevalence of asymptomatic Tropheryma whipplei carriage among humans and nonhuman primates. *J Infect Dis* 2008; **197**: 880-887

7 **Bai JC**, Mazure RM, Vazquez H, Niveloni SI, Smecuol E, Pedreira S, Mauriño E. Whipple's disease. *Clin Gastroenterol Hepatol* 2004; **2**: 849-860

8 **Durand DV**, Lecomte C, Cathébras P, Rousset H, Godeau P. Whipple disease. Clinical review of 52 cases. The SNFMI Research Group on Whipple Disease. Société Nationale Française de Médecine Interne. *Medicine* (*Baltimore*) 1997; **76**: 170-184

9 **Panegyres PK**. Diagnosis and management of Whipple's disease of the brain. *Pract Neurol* 2008; **8**: 311-317

10 **Fenollar F**, Amphoux B, Raoult D. A paradoxical Tropheryma whipplei western blot differentiates patients with whipple disease from asymptomatic carriers. *Clin Infect Dis* 2009; **49**: 717-723

11 **Sieg A**. Capsule endoscopy compared with conventional colonoscopy for detection of colorectal neoplasms. *World J Gastrointest Endosc* 2011; **3**: 81-85

12 **Gay G**, Delvaux M, Frederic M, Fassler I. Could the colonic capsule PillCam Colon be clinically useful for selecting patients who deserve a complete colonoscopy?: results of clinical comparison with colonoscopy in the perspective of colorectal cancer screening. *Am J Gastroenterol* 2010; **105**: 1076-1086

13 **Spada C**, Hassan C, Munoz-Navas M, Neuhaus H, Deviere J, Fockens P, Coron E, Gay G, Toth E, Riccioni ME, Carretero C, Charton JP, Van Gossum A, Wientjes CA, Sacher-Huvelin S, Delvaux M, Nemeth A, Petruzziello L, de Frias CP, Mayershofer R, Amininejad L, Dekker E, Galmiche JP, Frederic M, Johansson GW, Cesaro P, Costamagna G. Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011; **74**: 581-589.e1

14 ESGE research grants in ESGE Newsletter. *Endoscopy* 2010; **42**: 1119

15 **Keane MG**, Shariff M, Stocks J, Trembling P, Cohen PP, Smith G. Imaging of the small bowel by capsule endoscopy in Whipple's disease. *Endoscopy* 2009; **41** Suppl 2: E139

16 **Gay G**, Delvaux M, Frederic M. Capsule endoscopy in non-steroidal anti-inflammatory drugs-enteropathy and miscellaneous, rare intestinal diseases. *World J Gastroenterol* 2008; **14**: 5237-5244

17 **Dzirlo L**, Blaha B, Müller C, Hubner M, Kneussl M, Huber K, Gschwantler M. Capsule endoscopic appearance of the small-intestinal mucosa in Whipple's disease and the changes that occur during antibiotic therapy. *Endoscopy* 2007; **39** Suppl 1: E207-E208

18 **Feurle GE**, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. *Gastroenterology* 2010; **138**: 478-86; quiz 11-2

19 **Schneider T**, Moos V, Loddenkemper C, Marth T, Fenollar F, Raoult D. Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis* 2008; **8**: 179-190

S- Editor Song XX **L- Editor** Roemmele A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2012 December 16; 4(12): I
ISSN 1948-5190 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Endoscopy*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

Hongchun Bao, PhD, Research Fellow, the Center for Micro-Photonics, Faculty of Engineering and Industrial Sciences, Swinburne University of Technology, PO Box 218, Hawthorn, Victoria 3122, Australia

Simon Bar-Meir, Professor, Director, Department of Gastroenterology, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel

Hajime Isomoto, MD, PhD, Associate Professor, Department of Endoscopy, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Nevin Oruc, MD, Associate Professor, Ege University, Gastroenterology Department, Ege University Hospital, Bornova, İzmir 35100, Turkey

Krish Ragunath, Associate Professor, Consultant Gastroenterologist, Nottingham Digestive Diseases Centre and Biomedical Research Unit, Queens Medical Centre Campus, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, United Kingdom

Sema Zer Toros, MD, Department of Otorhinolaryngology/Head and Neck Surgery, Haydarpaşa Numune Education and Research Hospital, M.Saadettin Sk. Mecidiye Mh. Saadet Apt. No:3 D:4 Ortaköy/Beşiktaş, 34387 Istanbul, Turkey

Dr. Antonio Tucci, Gastrointestinal Unit, Castel S. Pietro Terme Hospital, University of Bologna, 40100 Bologna, Italy

Jochen Wedemeyer, MD, Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Carl Neuberg Str. 1, 30625 Hannover, Germany

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2012 December 16; 4(12): I
ISSN 1948-5190 (online)

Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA 94103, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
Kiev, Ukraine

October 4-6, 2012
EURO-NOTES 2012: NOTES and Advanced Interventional Endoscopy
Prague, Czech Republic

October 19-24, 2012
American College of Gastroenterology 77th Annual Scientific Meeting and Postgraduate Course
Las Vegas, NV 89085, United States

November 3-4, 2012
Modern Technologies in Diagnosis and Treatment of Gastroenterological Patients
Dnepropetrovsk, Ukraine

December 1-4, 2012
Advances in Inflammatory Bowel Diseases
Hollywood, FL 33028, United States

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2012 December 16; 4(12): I-V
ISSN 1948-5190 (online)

GENERAL INFORMATION

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253), is a monthly, open-access (OA), peer-reviewed online journal supported by an editorial board of 400 experts in gastrointestinal endoscopy from 45 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.

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 *WJGE* 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 *WJGE* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGE* 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 *WJGE* is to report rapidly the most recent results in basic and clinical research on gastrointestinal endoscopy including: gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy. Papers on advances and application of endoscopy-associated techniques, such as endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, endoscopic submucosal dissection and endoscopic balloon dilation are also welcome.

Columns

The columns in the issues of *WJGE* 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 endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (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 *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

Name of journal

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

Editor-in-Chief

Editorial Office
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381892
Fax: +86-10-8538-1893

Indexed and Abstracted in
PubMed Central, PubMed, Digital Object Identifier, 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
Statisital review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJGE* 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 comform 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, Ab stract, 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 International Committee of Medical Journal Editors to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-acces sible registry at its outset. The only register now available, to our knowledge, is http://www. clinicaltrials.gov sponsored by the Uni ted 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: wjge@wjgnet.com. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may

send an email describing the problem to http://www.wjgnet.com/esps/, or by telephone: +86-10-59080038. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

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

Title page

Title: Title should be less than 12 words.

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

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

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

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

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

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

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

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJGE*, 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, rapid communication and case reports, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5190/g_info_20100316080002.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**. Hyperten sion, 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/wjg/help/15.doc.

Abbreviations
Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing
Editorial: http://www.wjgnet.com/1948-5190/g_info_20100316080004.htm

Frontier: http://www.wjgnet.com/1948-5190/g_info_20100313155344.htm

Topic highlight: http://www.wjgnet.com/1948-5190/g_info_20100316080006.htm

Observation: http://www.wjgnet.com/1948-5190/g_info_20100107124105.htm

Guidelines for basic research: http://www.wjgnet.com/1948-5190/g_info_20100313155908.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-5190/g_info_20100313160015.htm

Review: http://www.wjgnet.com/1948-5190/g_info_20100107124313.htm

Original articles: http://www.wjgnet.com/1948-5190/g_info_20100107133454.htm

Brief articles: http://www.wjgnet.com/1948-5190/g_info_20100313160645.htm

Case report: http://www.wjgnet.com/1948-5190/g_info_20100107133659.htm

Letters to the editor: http://www.wjgnet.com/1948-5190/g_info_20100107133856.htm

Book reviews: http://www.wjgnet.com/1948-5190/g_info_20100313161146.htm

Guidelines: http://www.wjgnet.com/1948-5190/g_info_20100313161315.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of WJGE. The revised version including manuscript and high-resolution image figures (if any) should be re-submitted online (http://www.wjgnet.com/1948-5190office/). The author should send the copyright transfer letter, responses to the reviewers, English language Grade B certificate (for non-native speakers of English) and final manuscript checklist to wjge@wjgnet.com.

Language evaluation
The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form
Please download a Copyright assignment form from http://www.wjgnet.com/1948-5190/g_info_20100107134847.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/1948-5190/g_info_20100107134601.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
WJGE 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
WJGE is an international, peer-reviewed, OA, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.